UNMET NEEDS IN DYSTONIA

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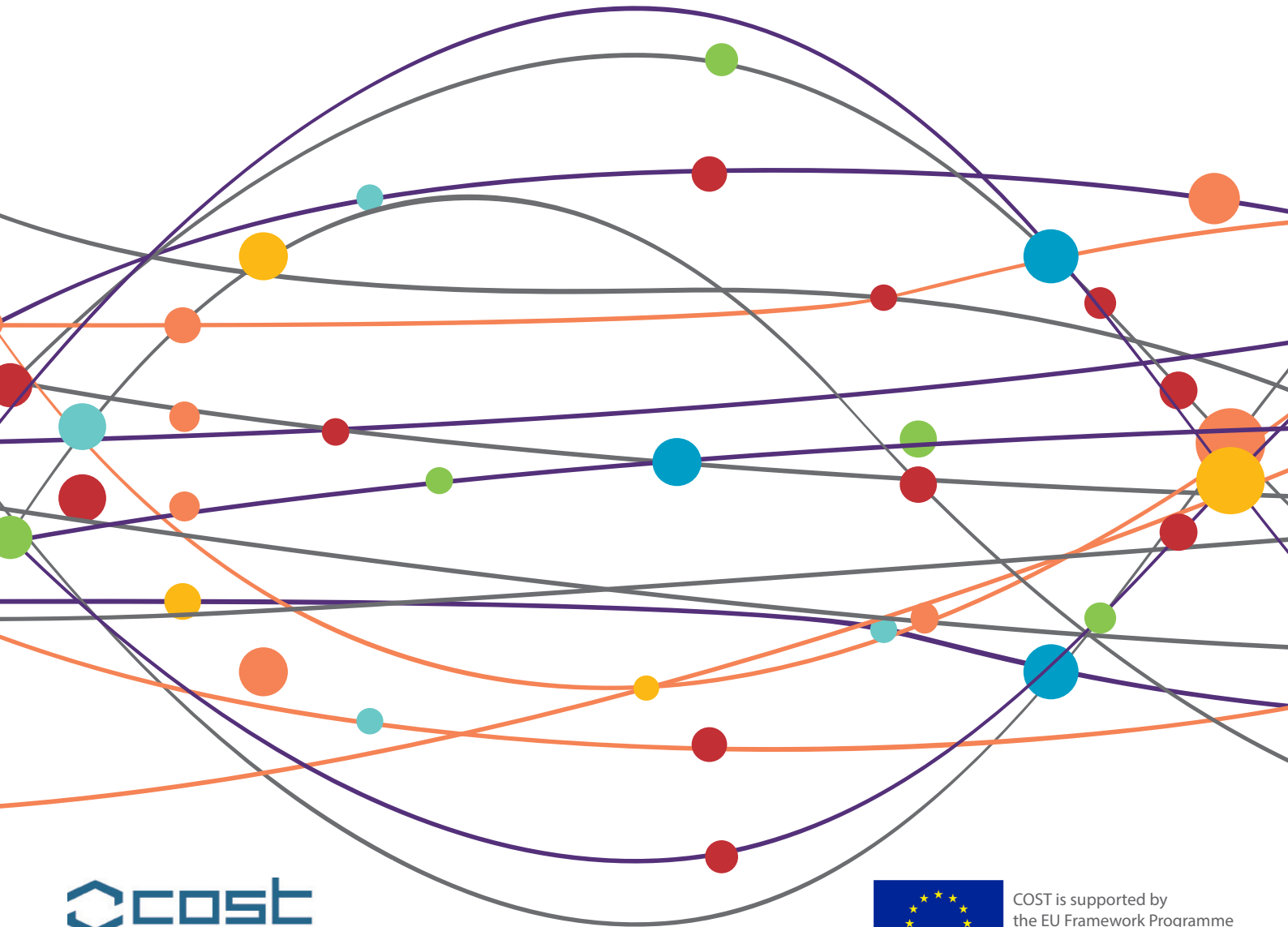

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UNMET NEEDS IN DYSTONIA

Topic Editor:
Alberto Albanese, Humanitas Research Hospital and Catholic University of the Sacred Heart Milano, Italy

This Research Topic contains proceedings of the final conference for COST Action BM1101 "European Network for the study of dystonia syndromes". The topic highlights consolidated knowledge and unmet needs in a field that is evolving very fast.

This publication is based upon work from COST Action BM1101, supported by COST (European Cooperation in Science and Technology).

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Participants at the "Unmet needs on dystonia" conference held in Rozzano on 16-17 October 2015 pictured on the campus of Humanitas Research Hospital. The participation of many young doctors and researchers has always characterized the activities of COST Action BM1101. Photo by Alberto Albanese

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EDITORIAL
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Editorial: Unmet Needs in Dystonia

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Keywords: dystonia, network, cooperation, lumping, splitting

The Editorial on the Research Topic

Unmet Needs in Dystonia

The need for a cooperation on dystonia at the European level has been pursued for years. This movement disorder has been extensively studied in Europe, where important advances in knowledge have repeatedly taken place. The pioneering clinical physiologic approach led by David Marsden has deeply characterized European research on dystonia and more recently the clinical and genetic complexity of dystonia has been clarified.

In 2011, the European Cooperation in Science and Technology (COST) office approved a European Concerted Research Action designated as COST Action BM1101: European network for the study of dystonia syndromes. The original applicants were from 18 European countries, but later increased to encompass 24 European countries and the United States. By the end of the Action, in 2015, the countries involved were: Belgium, Bulgaria, Croatia, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Republic of Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and United Kingdom. Clinicians and researchers from these countries have interacted on research and clinical activities during the 4-year duration of the Action. The European Dystonia Federation (now Dystonia Europe) has been a fundamental partner and has also served as administrative grant holder.

The European dystonia players have been deeply engaged by this concerted activity, and our research and personal ties have been reinforced along time. The Action has involved industry partners in additions to patients, doctors, and researchers. This research topic is the Action final publication, following a final conference held on October 2015 at the campus of Humanitas Research Hospital in Rozzano. The title "Unmet needs in dystonia" was proposed by Kailash Bathia and adopted by the Steering committee to signify the complexity of this area of knowledge that is still characterized by more questions than answers. We consider that this leitmotiv represents well the current state-of-art of dystonia.

The common theme of this publication is lumping vs splitting. How many dystonia syndromes exist clinically, genetically, neurophysiologically, etc.?

The first chapter in this Research Topic, by Albanese, is a clinical and historical review ending with a proposal on the new diagnostic criteria for dystonia syndromes. The descriptions of dystonia from post-medieval ages till now are reported. This exercise accounts for innovative clinical observations and scholar thinking. The second chapter by Verbeek and Gasser reviews the genetic heterogeneity of dystonia syndromes. Whole-exome sequencing and genome-wide association studies have allowed the discovery of novel genes and risk factors for dystonia. How to combine clinical and genetic heterogeneity is a matter for future research.

The third chapter by Valls-Sole and Defazio is an update on blepharospasm. Phenomenology and electrophysiology are reviewed for this simple, yet complex, focal dystonia. A chapter by Contarino et al. reviews the complex management of cervical dystonia, the most common focal dystonia syndrome. In this area, we expect several innovations, including treatment of non-motor features and functional neurosurgery. Evidence-based recommendations for the treatment of

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cervical dystonia with botulinum toxin are reviewed in the fifth chapter. Cervical dystonia is an area where we expect most innovation in management with botulinum neurotoxins. Injection of deep cervical muscles, usage of ultrasound, and EMG combined are rewriting current clinical practice. The next chapter by Lin and Nardocci reviews the complex issue of childhood dystonia that is often combined with other movement disorders or neurodevelopmental issues. Finally, the needs and requirements of modern biobanks, an issue extensively discussed within the COST Action, are reviewed by Lohmann et al.

We hope that these contributions will be helpful to clinicians, researchers, and patients. Altogether they offer a glimpse on dystonia that is not available elsewhere.

This effort (and all the activities covered by the COST Acton) have been possible thanks to the dedication of Alistair Newton and Monika Benson (from Dystonia Europe), who deserve all our thanks. Their long-standing friendship under the name of dystonia and their stubborn dedication turned so many common initiatives, including this COST Action, into a success. The author also wish to thank the COST Office (now COST Association) and particularly Inga Dadeshidze and Jeannette Nchung Oru, who assisted us as Science and Administrative Officers.

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The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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How Many Dystonias? Clinical Evidence

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Literary reports on dystonia date back to post-Medieval times. Medical reports are instead more recent. We review here the early descriptions and the historical establishment of a consensus on the clinical phenomenology and the diagnostic features of dystonia syndromes. Lumping and splitting exercises have characterized this area of knowledge, and it remains largely unclear how many dystonia types we are to count. This review describes the history leading to recognize that focal dystonia syndromes are a coherent clinical set encompassing cranial dystonia (including blepharospasm), oromandibular dystonia, spasmodic torticollis, truncal dystonia, writer's cramp, and other occupational dystonias. Papers describing features of dystonia and diagnostic criteria are critically analyzed and put into historical perspective. Issues and inconsistencies in this lumping effort are discussed, and the currently unmet needs are critically reviewed.

Keywords: dystonia, movement disorders, history, definition and concepts, phenomenology

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LITERARY DESCRIPTIONS OF DYSTONIA

Dystonia has been defined by Denny-Brown as "the most striking and grotesque of all neurological disorders" (1). Therefore, it is not surprising that artists have reported the feature of dystonia before doctors were able to categorize its striking phenomenology. Cervical dystonia, the most prevalent dystonia type, has been the object of some famous literary portrayals. The first artistic description dates back to 1315, when Dante Alighieri reported having seen fortune tellers and diviners punished in the Inferno (Circle eight, *Bolgia* four), by the divine law or retaliation for having looked too far forward, with their head twisted backwards (2):

> And when I looked down from their faces, I saw
> that each of them was hideously distorted
> between the top of the chest and the line of jaw;
> for the face was reversed on the neck, and they came on
> backwards, starting backwards at their loins,
> for to look before them was forbidden. Someone
> sometime, in the grip of palsy may have been
> distorted so, but never to my knowledge;

Rabelais (circa in 1532) introduced the French neologism torticollis (*torty colly* in the original old French). Into a similar infernal atmosphere, he described the healing of Epistemon, "who had

his head cut off, was finely healed by Panurge, and brought news from the devils, and from the damned people in hell" … "Thus as they went seeking after him, they found him stark dead, with his head between his arms all bloody" … "Panurge took the head and held it warm foregainst his codpiece, that the wind might not enter into it. Eusthenes and Carpalin carried the body to the place where they had banqueted, not out of any hope that ever he would recover, but that Pantagruel might see it. … Then cleansed he his neck very well with pure white wine, and, after that, took his head, and into it synapised some powder of diamerdis, which he always carried about him in one of his bags. Afterwards he anointed it with I know not what ointment, and set it on very just, vein against vein, sinew against sinew, and spondyle against spondyle, that he might not be torticollis (for such people he mortally hated). This done, he gave it round about some fifteen or sixteen stitches with a needle that it might not fall off again; then, on all sides and everywhere, he put a little ointment on it, which he called resuscitative."

Other artists have described focal dystonias, particularly cervical dystonia, but not as much the generalized cases, that may have appeared too severe to become a narrative subject.

EARLY MEDICAL DESCRIPTIONS

It is of interest to follow the historical order by which different dystonia types were recognized and described. It is also remarkable to note how some fundamental clinical questions have remained actual, and for the most unanswered, until now.

Cervical Dystonia

Cervical dystonia has attracted early medical interest. Tulpius (3) gave one of the first descriptions of torticollis; he considered a contraction of the scalene muscles as the most common cause. A first classification was attempted by Heister (4), who distinguished "caput obstipum" from "collum obstipum," a phenomenological distinction that has been recently proposed anew (5). A prominent role of the sternocleidomastoid muscle was later widely recognized and surgical sections of its tendons started being performed by orthopedic surgeons. A non-surgical approach, based on head repositioning under anesthesia followed by head bandage, later gained diffusion in France and abroad as an alternative to surgical ablations (6). This approach attracted a wide medical audience interested in the management of "muscular torticollis" (then distinguished from torticollis caused by scars or bone anomalies; **Table 1**). The monumental medical encyclopedia edited by Dr. Fabre reported: "It appears today that the majority of neck muscles may become the starting point of a permanent retraction and may also contribute to some type of head deviations" (7). The complex phenomenology of torticollis was also recognized: "the sternocleidomastoid is not the only muscle that may be involved; the majority of other cervical muscles may be involved, so to produce the attitude of torticollis either by their specific action or by a combined influence" (8). Torticollis became then a matter for neurologists. Pitres recognized that there was no pathognomonic sign to distinguish spasms of hysteric origin from the non-hysteric ones (9). The non-hysterical nature of torticollis was reinforced by the observation that patients with torticollis also had "functional spasms" in other body regions (10).

TABLE 1 | Classification of cervical dystonia by the end of nineteenth century (11).

Etiology	• Cicatricial torticollis	Retraction of skin and subcutaneous tissue following burn, abscess, phlegmon, etc.
	• Muscular torticollis	Muscular abnormality caused by contraction, retraction (often congenital), paralysis, and spasm (intermittent or spasmodic)
	• Articular (or osseous) torticollis	Abnormality of joints or cervical vertebrae
Onset	• Congenital • Acquired	
Phenomenology	• Anterior • Posterior • Lateral	

Cicatricial torticollis was considered very common, as it was often observed in soldiers returning from battlefields.

Generalized Dystonia

Generalized dystonia was listed for the first time by Gowers under the name of "tetanoid chorea," one of the several choreatic disorders encompassing also senile chorea, maniacal chorea, functional chorea, and Sydenham's chorea (12). He had probably also observed idiopathic generalized cases, but later defended that "tetanoid chorea" was a feature of Wilson's disease (13).

Undoubtedly, 1911 is the founding year of generalized dystonia as an independent nosological entity. Hermann Oppenheim, probably the most famous German neurologist of the time, published the description of *dystonia musculorm deformans* (altered muscle tone causing deformities), a condition he observed in four unrelated Jewish children who came to Berlin to be seen by him (14). He also added a second Latin descriptor *dysbasia lordotica progressiva* (progressive gait difficulty with lordosis), as he noted the occurrence of pronounced and progressive lordosis in his patients. A similar phenomenology had been previously observed in a Jewish kindred by Theodor Ziehen, professor of psychiatry in Berlin, who asked his resident Markus Walter Schwalbe to write a dissertation on this peculiar phenomenology. Ziehen presented his observations in Berlin in December 1910 and published the family in 1911 as well (15). Finally, Edward Flatau and Wladyslaw Sterling described the same condition observed in two Polish Jews under the name of "progressive torsion spasm" in 1911 as well (16).

Unquestionably, Oppenheim's publication is the most prominent of the three. Patient 1 described by Flatau and Sterling was also seen by Oppenheim himself, and Flatau and Sterling repeatedly mention Oppenheim's seminal publication. Both Oppenheim and Flatau and Sterling underline the organic nature of the disease and reject Schwalbe–Ziehen's label of hysterical disorder. Their reasoning is however different. Oppenheim considered the phenomenology of Schwalbe–Ziehen's cases different from that of *dystonia musculorum deformans* he was

describing. He reported: "I find profound differences between these observations and those of my own, also with respect to the account of this affliction given by Ziehen himself. Hence, Schwalbe describes choreiform and tic-like movements." Flatau and Sterling, instead, used clinical arguments to reject the hysterical nature of the phenomenology they had observed. They reported: "The first boy we first saw in 1909 offered us great diagnostic difficulties. Some colleagues, to whom we presented the case in the hospital, thought of hysteria. We have, however, denied this diagnosis in a more precise analysis, and considered the case as an unknown form of spasm. The longer we have observed the patient, the deeper was the conviction that we were not dealing with any functional disease, but with a disease of its own" … "The clinical picture was so characteristic that when one of us saw the second case in his office, he immediately thought of his similarity with the first."

The clinical descriptions in Flatau–Sterling publication are particularly interesting, probably because they have appeared later than Oppenheim's publication. Oppenheim defended that: "the clonic jerks do indeed belong to the clinical picture," "the hypotonia is a major element of the symptomatology," and "the tonic cramps are very predominantly connected with the function of standing and walking." Hence, he proposed to name the disease "dystonia" (i.e., abnormal muscle tone) or "dysbasia" (i.e., abnormal base while standing or walking). Flatau and Sterling reasoning led them to dispute this terminology. They stated: "With the name suggested by Oppenheim (*Dysbasia lordotica progressiva* and *Dystonia musculorum deformans*), we cannot be satisfied for the reason that in some, such as our two patients, the disease is as strong in the upper as in the lower extremities, and dysbasia is not the principal symptom. We have also shown that there is no hypotonia in our patients, and we also believe that the word 'deformans' contains something stable, which is not true in the case of the essentially mobile spasm."

Numerous reports followed. In a review of all published cases, Mendel summarized the significant clinical data and introduced the expression "torsion dystonia" to indicate a specific nosologic entity distinguished from other types of involuntary movements, such as hysteria, double athetosis, chorea, and myoclonus (17). During the following decades, different types of hyperkinetic movements (including dystonia) were reported in patients with encephalitis lethargica, Wilson's disease, or cerebral palsy (then called double athethosis). The issue whether dystonia was a disease entity or instead a syndrome of basal ganglia dysfunction with different possible causes arose. Dystonia became the topic of some dedicated symposia where similarities between focal and generalized dystonia types were mentioned. At the 95th Annual Meeting of the British Medical Association held in Edinburg in 1927, a session was devoted to the "existing confusion on involuntary movements." Guillain there defended the view that torticollis was not a psychogenic condition (18). In 1929, a session of the Tenth French Congress of Neurology was devoted to "torsion spasms," with lively discussions about their psychiatric vs. organic origin (19). This issue was gradually settled by the observation that torticollis and torsion spasms (initially defined as pseudo-parkinsonism) could be secondary to encephalitis lethargica (20). In 1940, the Association for Research in Nervous and Mental Diseases extensively discussed the phenomenology of dystonia, its similarity with athetosis, the related EMG reading, and the underlying pathology (21). According to Herz (21), the term *dystonia musculorum deformans* should be confined to the idiopathic form. He gave the following criteria for the clinical diagnosis of idiopathic dystonia: (a) selective systemic symptoms in the form of dystonic movements and postures; (b) gradual development, without recognizable etiological factors at the onset. He also distinguished early forms occurring shortly after birth, from the juvenile form with the onset between 5 and 15, and the late form after 15 years of age.

Other Focal Dystonias

Notwithstanding these scholarly observations, torticollis and generalized dystonia were still considered two separate and distinct conditions. Craft neuroses (also called occupational spasms or trade palsies) were also considered a distinct group of "functional disorders which are characterized by a difficulty in performing specific coordinated movements of certain occupations" (22). The best known craft neuroses were writer's cramp and telegraphists' cramp.

Writer's cramp was another medical condition known since 1700 from the work of Bernardino Ramazzini, the father of occupational medicine (23), who stated: "The diseases of persons incident to this work arise from three causes; firstly, constant sitting, secondly the perpetual motion of the hand in the same manner, and thirdly the attention and application of the mind. Constant writing considerably fatigues the hand and whole arm on account of the almost continual and almost tense tension of the muscles and tendons." In the mid-nineteenth century, Duchenne (24) and Gowers (25) wrote extensively about writer's cramp. Solly provided an early surgeon's view and considered writer's cramp a spinal cord disorder (26). The largest early series was published by Poore (27), whose classification was based on tenderness and measures of faradic response. A comprehensive monograph on telegraphists' cramp was written by Cronbach (28), who described 17 cases which he had observed in Berlin.

Eye and facial spasms were a yet different condition. A notable artistic description of cranial dystonia was likely provided circa in 1558 by the vivid painting of an elderly woman made by Pieter Brueghel (29). The first medical description of blepharospasm was given in 1906 by a French ophthalmologist (30). Meige is credited to have described cases of blepharospasm and other cranial dystonias (31). Patients had predominantly symmetric dystonic spasms of facial muscles, sometimes associated with dystonic movements of other midline muscle groups. After the original description, little appeared in the literature until 1972, when there were reports of isolated oromandibular dystonia (32) and oromandibular dystonia with blepharospasm (an association then described with the eponym "Meige's syndrome") (33). Marsden later used the expression "Brueghel syndrome" to describe a large series of patients and noted that it usually started in the sixth decade with blepharospasm, oromandibular dystonia, or both. Meige's syndrome later became the preferred expression (34).

Spasmodic dysphonia was probably first described by Traube in the second volume of his textbook (35) and later by Meige (36) and by Macdonald Critchley, who argued whether to call it "spastic" or "dystonic" dysphonia (37). These two terminologies have been used interchangeably until very recently.

LUMPING FOCAL DYSTONIAS TOGETHER

Genetic Studies

The first glimpse to a possible connection among different focal dystonia syndromes was the observation that two patients with "spasmodic torticollis" also had "functional spasms" in other body regions, including the right thigh, the upper limb while writing (writer's cramp) and the left foot (10). A second contribution toward lumping together different types of spasms came by the observations that ablative surgery was helpful in focal and generalized dystonia regardless of its etiology (38, 39).

Zeman et al. (40) summarized very neatly the features of idiopathic dystonia: "The chief symptoms are dystonic postures and dystonic movements. The latter are true hyperkinesias and are characterized by relatively slow, long-sustained, powerful, nonpatterned, contorting activities of the axial and appendicular muscles. The muscles most commonly involved are those of the neck, trunk, and proximal portions of extremities. Involvement of unilateral muscle groups often results in bizarre torsion movements, hence the alternative term 'torsion dystonia' for the disease." … "'Dystonic posture' is the term used if the end position of a dystonic movement is maintained for any length of time. Eventually this may lead to contracture deformities." Zeman et al. (40) reviewed the published cases with autosomal dominant or recessive transmission and distinguished these from sporadic ones. They reported a four-generation family with autosomal dominant inheritance and so discussed phenotypic heterogeneity.

"Within this family there is a considerable variability of expressivity of the disease. For instance, V-14 shows symptoms of dystonia in a very mild form, manifested by temporary limping, torticollis and blepharospasm. At times this patient appears almost normal. On the other hand, three of his siblings are totally crippled and helpless. V-10 has neither spontaneous movements nor the typical dystonic posture. Yet, upon performing certain volitional movements, typical dystonic features can be easily elicited. Certainly in cases like these two, one could take the position that such manifestations do not justify the diagnosis of dystonia. Yet, it would be illogical to consider any other diagnosis in view of the fact that grandmother, father, siblings, and one child are so definitely affected by dystonia. Applying 'Occam's razor' of scientific parsimony, it is certainly the most logical conclusion that this family exhibits 'formes frustes' as well as full-fledged cases of dystonia. Obviously, the strict diagnostic criteria as set forth by Herz (21) were not applied to the subject cases." It was then recognized that "idiopathic torsion dystonia" is a genetic disorder with heterogeneous phenomenology, from focal to generalized within a same family.

The following years witnessed the development of stereotactic and functional neurosurgery, which was applied to dystonia as well as to Parkinson's disease. At the same time, there were attempts to understand and classify the diverse causes of dystonia. Levodopa, the newly discovered treatment for Parkinson's disease, was also tried in dystonia (41). Denny-Brown (42) did not contribute much to understanding the phenomenology of dystonia, although he attempted to distinguish dystonia occurring in Huntington's chorea, athetosis, dystonia musculorum deformans, and parkinsonism. He described possible anatomical correlates of each of these dystonia syndromes; he also performed brain lesions in monkeys and called "dystonia" whatever postural phenomenon he could observe, including postural abnormalities associated with spastic hemiplegia ("cortical dystonia").

In 1966, Jacob A. Brody, Chief of Epidemiology Branch at NINDS, and Irving S. Cooper, Head of Neurologic Surgery at St. Barnabas Hospital, discussed possible epidemiologic studies utilizing the large population of patients with neurological diseases seen at St. Barnabas Hospital over the years. During the course of their talks, Dr. Cooper mentioned that he had operated on approximately 200 patients with torsion dystonia. Dr. Roswell Eldridge, a trained medical geneticist, had just joined Dr. Brody's staff, and he sensed a fertile ground for a genetic study of this disease. He then gathered a body of information on torsion dystonias, which provided important insights on the various genetic forms of the disease, their clinical presentation, and geographic and ethnic patterns. On January 9, 1970, Dr. Roswell Eldridge convened a conference on the torsion dystonias at NIH in Bethesda, MD, USA.

Clinical Observations

When he moved from St. Thomas's Hospital to King's College in 1970, David Marsden was already interested in the pathophysiology of movement and had studied the physiology of human tremor. In 1973, he gave a lecture on drug treatment of diseases characterized by abnormal movements at a symposium on "Involuntary movements other than parkinsonism" (43). On that occasion, he reported that "chorea (including hemiballism and orofacial dyskinesia) and generalized torsion dystonia may be considered together, for the abnormal movements of both can be reduced by the same groups of drugs, although neither can be cured," and that "spasmodic torticollis must also be mentioned briefly, for it is a common problem." He later became fascinated by dystonia, an involuntary movement with irregular features compared to tremor and with unknown pathophysiology.

In his publication dedicated to the review of 42 patients with dystonia, Marsden recognized that "idiopathic torsion dystonia (dystonia musculorum deformans) is a rare and fascinating disease" (44). This paper contains all the elements for considering dystonia a unique disease. He used Herz's diagnostic criteria (21) and distinguished three types of onset: the commonest being a difficulty to use one or both arms, the second commonest was an abnormality of gait, whereas in a minority of patients, the initial abnormality was confined to the neck and trunk. In half of the patients, the disease progressed to involve all the limbs and trunk, and in the remaining half,

the disease was confined to one portion of the body and never became generalized. Marsden still considered cervical dystonia a separate entity and stated: "the characteristic features of torsion dystonia in adults is that it is usually restricted to one part of the body and that it is usually non-progressive. In these respects adult-onset torsion dystonia strikingly resembles isolated spasmodic torticollis, which we deliberately excluded from the study" (44).

In 1975, Marsden attended the first international conference on dystonia that was convened in New York by Roswell Eldridge and Stanley Fahn. Compared to the conference held in Bethesda 5 years before, this was called international as the faculty originated also from outside the United States. Stanley Fahn, who was at Columbia University in New York, had seen the daughter of Samuel and Frances Belzberg who was affected by generalized dystonia and consulted with Dr. Eldridge, who had extensively reviewed the genetic epidemiology of dystonia at the 1970 conference (45). The Belzberg family supported the creation of the Dystonia Foundation (today Dystonia Medical Research Foundation) and the 1975 international symposium. Stanley Fahn was particularly interested in the phenomenology and classification of dystonia and defended the view that dystonia was a symptom of several different dystonic syndromes, which he attempted to classify (46). At the same meeting, Marsden reported on "the problem of adult-onset idiopathic torsion dystonia and other isolated dyskinesias in adult life (including blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis, or axial dystonia)" (47). The slide he showed lumping together blepharospasm, orofacial dystonia, writer's cramp, torticollis, truncal dystonia, and leg dystonia was quite visionary (**Figure 1**). He probably drafted it at one of the afterhours meetings with his assistants and fellows at The Phoenix and Firkin pub in Denmark Hill (48).

The founding of the modern concept of dystonia is considered to have occurred exactly 40 years ago, in 1976, when David Marsden published several reports on dystonia (50–53). One of these accounts, in particular, suggested that blepharospasm could be a variant of adult-onset focal dystonia (53). This was a striking notation, not only due to the vivid picturing of *De Gaper*, by Pieter Brueghel the Elderly; but also because blepharospasm had not previously entered the spectrum of dystonia, and was not considered a phenomenology of *formes frustes* or a body part involved in generalized dystonia. Marsden concluded that "(1) blepharospasm and oromandibular dystonia are manifestations of a single illness or syndrome; (2) this is a physical illness, not a manifestation of a psychiatric disorder; (3) this syndrome is related to idiopathic torsion dystonia."

In the following years at Denmark Hill, the interest in myoclonus melted with that of dystonia and spanned from phenomenology to physiology and experimental animal models. Chorea and dystonia were recognized in patients with Parkinson's disease (54, 55). Primary writing tremor was described as a condition independent of "myoclonic jerks occurring in dystonia" and of "benign essential tremor" (56).

In 1981, an *ad hoc* committee established by the Research Group on Extrapyramidal Disorders of the World Federation of Neurology, chaired by André Barbeau (including David Marsden, but not Stanley Fahn) proposed that "hyperkinesias" encompassed tremors, tics, myoclonus, chorea, ballism, athetosis, and akathisia (57). Dystonia was listed under "disorders of posture and tone" aside "torsion spasm," cogwheel phenomenon, hypertonia (encompassing rigidity and Gegehalten), and hypotonia. This classification did not have follow-up. By the same time, in a parallel publication Marsden listed chorea, dystonia, tremor, myoclonus, and tics under the collective heading of dyskinesias, as distinguished from rigid-akinetic syndromes (58). In a celebrated Robert Wartenberg lecture, delivered in April 1981 in front of the American Academy of Neurology, David Marsden summarized his vision of basal ganglia functions by putting together pathophysiology, anatomy, nosology, and phenomenology (49). Around that time, he conceived and crafted along with Stanley Fahn the intellectual and practical infrastructure

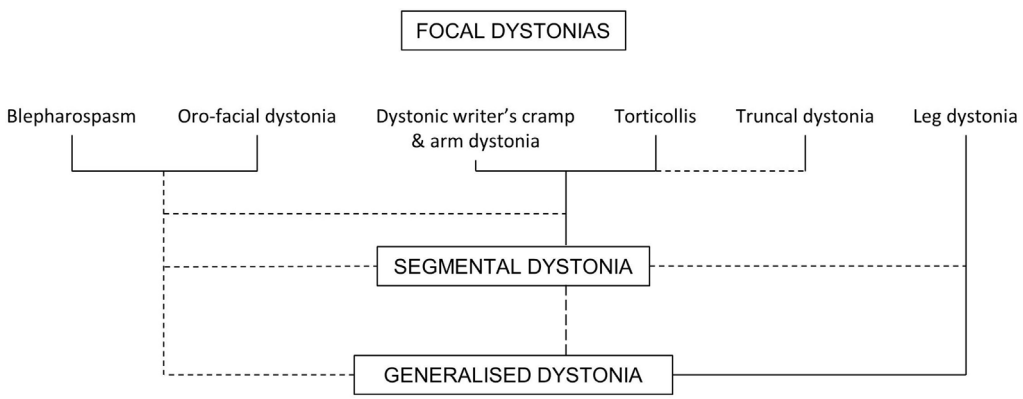

FIGURE 1 | "Possible interrelations between blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis/axial dystonia (focal dystonias), and idiopathic torsion dystonia of segmental or generalized type. Common associations are shown by solid lines, and rare transitions by dashed lines" modified from (47). Marsden's handwritten schemes can be found also in other publications, such as the Roberg Wartenberg lecture (49) or the Phoenix and Firkin beermats (48).

TABLE 2 | Features observed in dystonia and diagnostic criteria for different dystonia types have evolved over time.

Year	Features	Applies to	Reference
1944	• Dystonic movements: slow, long-sustained turning movements of the head and trunk and rotations of the upper or lower extremities. Show a still more pronounced excess of tension, which prevails over the excess of motion. • Dystonic postures: peculiar positions, which occur in various combinations. Show the influence of excess of tension in almost pure form.	Generalized dystonia (symptomatology)	(21)
1956	Involuntary tonic but spasmodic bilateral contraction of the orbicularis oculi, in which the spasm of the eyelids may last from several seconds to several minutes, with periods of relaxation of varying length interspersed	Blepharospasm	(68)
1959	• The chief symptoms are dystonic postures and dystonic movements • The muscles most commonly involved are those of the neck, trunk, and proximal portions of extremities	Dystonia in general	(40)
1974	An illness characterized by the development of dystonic movements and postures	Generalized dystonia (idiopathic torsion dystonia, dystonia musculorum deformans)	(44)
1982	Definitions • Simple cramp: difficulty performing only one specific task • Dystonic cramp: muscle spasms in several tasks • Progressive cramp: increasing difficulty in performing new tasks Associated neurological signs • Tremor • Increased limb tone • Decreased arm swing • Dystonic posture	Upper limb dystonia (writer's cramp, typist's cramp, pianist's cramp)	(62)
1984	Description of the varied phenomenology of "rapid" dystonic movements occurring in different body regions: upper face, lower face, jaw, pharynx, tongue, neck, arm, trunk, leg, segmental, generalized (in addition to the description of slow dystonic movements by Herz) (21)	Dystonic movements	(69)
1988	Elements identified by physiologic investigation that are indicative of impaired motor control in dystonia • Co-contraction of antagonist muscles • Prolongation of EMG bursts • Tremor • Lack of selectivity in attempts to perform independent finger movements • Failure of willed activity to occur	Upper limb dystonia	(70)
1988	A syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures	Dystonia in general	(71)
1988	Repetitive involuntary sustained contractions of orbicularis oculi Increased blinking frequently is the first sign of blepharospasm	Blepharospasm	(72)
1991	Presenting symptoms: pulling in the neck (59%), head tremor (14%), neck pain (17%), head jerking (11%), neck stiffness/tightness (7%), a combination of any two of these symptoms (18%)	Cervical dystonia	(73)
1991	Pain is a specific feature of cervical dystonia	Cervical dystonia	(74)
1994	In addition or as an alternative to typical spasm of the orbicularis oculi, there may be failure to voluntarily open the eyes with no apparent spasm of the orbicularis oculi (sometimes called "apraxia" of eyelid opening)	Blepharospasm	(75)

(*Continued*)

TABLE 2 | **Continued**

Year	Features	Applies to	Reference
1997	• Dystonia: dystonic posturing and slow torsion movements are evident to all the examiners. • Blepharospasm: all the examiners find at least two prolonged spasms of the orbicularis oculi muscles. • Writer's cramp: at least three of the following occur: (1) a progressive change in handwriting, (2) a progressive change of handgrip, (3) hand posturing and increased pressure on the sheet during handwriting, (4) abnormal contraction of brachia! or antebrachial muscles during handwriting, and (5) hand posturing associated with abnormal proximal movements of the arm or shoulder while writing.	Dystonia syndromes (definite diagnosis for family study)	(76)
2000	Distinguishing clinical features of dystonia • Speed of contractions may be slow or rapid, but at the peak of movement, it is sustained. • Contractions almost always have a consistent directional or posture assuming character. • Predictably involves one or more body regions. • Usually aggravated during voluntary movement (action dystonia) and may only be present with specific actions (e.g., writing); alternatively certain actions may improve dystonia—known as paradoxical dystonia (e.g., speaking often improves oromandibular dystonia). • May progress to involve more body regions and more actions, eventually involving rest. • Usually varies with changes in posture. • Worse with stress, fatigue; better with rest, sleep, and hypnosis. • Sensory tricks (tactile or proprioceptive maneuver) lessen contractions (touching cheek improves torticollis).	Dystonia in general	(77)
2002	• Definite dystonia: characteristic overt twisting or directional movements and postures that are consistently present. • Probable dystonia: postures or movements suggestive of dystonia that are insufficient in intensity or consistency to merit classification as definite (e.g., excessively tense and labored writing with minimal posturing, flurries of blinking, but no episodes of sustained closure, mild or intermittent head deviation). • Possible dystonia: muscle contractions not considered abnormal but remotely suggestive of dystonia (e.g., unusual hand grip with mild excess hand tension but normal flowing handwriting, increased blinking with no flurries or sustained contractions, clumsy rapid feet movements with intermittent overflow toe posturing). Scoliosis and regular tremor (i.e., without sustained directionality) were not considered signs of dystonia for any category	Dystonia signs and symptoms observed in different subjects of affected families	(78)
2003	In dystonic hypertonia, all of the following are expected • Resistance to externally imposed joint movement is present at very low speeds of movement, does not depend on imposed speed, and does not exhibit a speed or angle threshold. • Simultaneous co-contraction of agonists and antagonists may occur, and this is reflected in an immediate resistance to a rapid reversal of the direction of movement about a joint. • The limb tends to return toward a fixed involuntary posture, and when symptoms are severe, the limb tends to move toward extremes of joint angles. • Hypertonia is triggered or worsened by voluntary attempts at movement or posture of the affected and other body parts and may be strongly dependent on the particular movement or posture attempted or the activity of distant muscle groups. • The pattern as well as the magnitude of involuntary muscle activity varies with arousal, emotional and behavioral state, tactile contact, or attempted task. • There is no other detected spinal cord or peripheral neuromuscular pathology causing tonic muscle activation at rest.	Dystonic hypertonia in children	(79)
2004	Clinical diagnostic criteria • Identified kinesigenic trigger for the attacks • Short duration of attacks (1 min) • No loss of consciousness or pain during attacks • Exclusion of other organic diseases and normal neurologic examination • Control of attacks with phenytoin or carbamazepine, if tried • Age at onset between 1 and 20 years, if no family history of PKD	Paroxysmal kinesigenic dyskinesias	(80)
2006	Dystonia is a movement disorder characterized by patterned, directional, and often sustained muscle contractions that produce abnormal postures or repetitive movements	Dystonia in general	(81)

(*Continued*)

TABLE 2 | **Continued**

Year	Features	Applies to	Reference
2006	Blink rate at rest >27 blinks/min and higher than blink rate during conversation suggests a diagnosis of blepharospasm, whereas blink rate during conversation higher that blink rate at rest suggests against such diagnosis	Blepharospasm	(82)
2008 (and 2009)	Features of "ipsilateral overflow" and "contralateral overflow," as distinct from features of "mirror dystonia"	Upper limb dystonia	(83, 84)
2009 (and 2016)	• Dystonic postures: a body part is flexed or twisted along its longitudinal axis; slowness and clumsiness for skilled movements are associated with sensation of rigidity and traction in the affected part. • Dystonic movements: either fast or slow; tremor is a feature of dystonic movements and may appear as isolated tremor; movements are repetitive and patterned (i.e., consistent and predictable) or twisting, and often sustained at their peak to lessen gradually in a preferred posture (usually opposite to the direction of movement). • Gestes antagonistes (sensory tricks): voluntary actions performed by patients that reduce or abolish the abnormal posture or the dystonic movements. • Mirror dystonia: a unilateral posture or movement with same or similar characteristics to the patient's dystonia that can be elicited, usually in the more severely affected side, when contralateral movements or actions are performed. • Overflow dystonia: an unintentional muscle contraction accompanying the most prominent dystonic movement, but in an anatomically distinct neighboring body region.	Dystonia (physical signs) excluding cranial and laryngeal forms	(85, 86)
2011	Specific criteria: observation of involuntary bilateral increased blinking with intermittent eye spasms Patients were also asked about photophobia, dry eyes, and sensory tricks. If present, these symptoms were helpful to make the diagnosis; however, they were not deemed essential	Blepharospasm	(87)
2013	Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation	Dystonia in general	(88)
2013	• Stereotyped, bilateral, and synchronous orbicularis oculi spasms inducing narrowing/closure of the eyelids • Effective sensory trick • Increased blinking	Blepharospasm	(89)
2014	List of sensory tricks observed in different dystonia types	Different dystonia types	(90)

This table lists diagnostic criteria and clinical features that have been proposed to be specific for different dystonia types. Clinical series that did not specifically mention diagnostic criteria for dystonia, classifications schemes, and rating tools are not listed here.

for the current thinking on dystonia and other movement disorders. Together, they discerned and promulgated the critical clinical characteristics that distinguish dystonia from other involuntary movements (59).

The focal dystonias were then lumped together, as a coherent clinical set encompassing cranial dystonia (including blepharospasm), oromandibular dystonia, spasmodic torticollis, truncal dystonia, writer's cramp, and other occupational dystonias (60). Specific publications were dedicated to characterize this newly defined large set of organic diseases called dystonias: "spastic dysphonia" (61), writer's cramp (62), myoclonus dystonia (63), and tardive dystonia (64). At the same time, neurophysiological studies aimed to identify a common pathophysiology for the dystonia syndromes: a quite challenging task (65, 66).

CURRENT VIEWS

Is dystonia one or many diseases? The lucid effort of lumping together conditions that were previously considered separate diseases has greatly contributed to the modern era of movement disorders but has left unsolved the issue of whether dystonia is to be regarded today as a single disease entity, a syndrome, a collection of physical signs, or as a somehow heterogeneous collection of syndromes. The cases for lumping different dystonias into a unique disease entity, or by the contrary to split them into separate conditions, have been the object of a recent review (67). There is no unique etiology or pathophysiology for different dystonia syndromes and—although a number of features clearly overlap—we have to admit that clinical features, etiology, and pathophysiology are heterogeneous. Dystonia still remains a mysterious condition notwithstanding a dramatic increase in knowledge.

Table 2 summarizes the evolution of observed clinical features of dystonia syndromes. Some observations have been retained over time, the most solid one being the recognition of dystonic movements and postures as the hallmarks features of dystonia, as noted by Herz's cinematic studies (21). Some observations deal with dystonia in general, while others list features and diagnostic criteria for specific focal dystonia types. These two viewpoints do not necessarily overlap.

Ten papers considered the general features of dystonia, defined as a disease, a syndrome, or a collection of physical signs (**Table 2**). Herz (21) was the first to define diagnostic criteria for dystonia that have been updated in recent years by recognizing five main physical signs of dystonia (85, 86) that can be reliably recognized when the limbs or the neck/trunk are affected. By contrast, these features are difficult to assess in patients with blepharospasm, which has a different phenomenology, or spasmodic dysphonia, where the abnormal movements are hard to see. The five physical signs of dystonia encompass dystonic postures, dystonic movements, tricks/gestes, mirror dystonia, and overflow. When several of these signs occur together in the same patient, a diagnosis of dystonia can be reliably made. As for other medical diagnoses, not all the physical signs have to occur simultaneously, but they need to be in sufficient number to provide a strong diagnostic clue. Some of the general diagnostic criteria for dystonia have been developed for the study of affected families using linkage studies, where the affected or non-affected status provided a discriminant variable (76, 78). In these families, focal phenotypes were considered alternative phenotypes or *formes frustes* of a same genetic condition.

Six publications defined the features and diagnostic criteria of blepharospasm. This focal form has different features from dystonia affecting the limbs or trunk. Diagnostic criteria for blepharospasm have been proposed only recently, and their specificity is a matter of discussion (89). Four publications reported diagnostic features of upper limb dystonia, and two (unlisted) studied assessed lower limb dystonia without indicating diagnostic criteria (91, 92). It is interesting to note that very few publications have tried to list diagnostic features of cervical dystonia, which is still diagnosed based on clinical experience and often considered an easy diagnostic task.

The swing is currently moving back toward recognizing the specific identity of focal dystonia syndromes. A Delphi method approach is being used by the Movement Disorders Society Dystonia Task Force to identify specific criteria for blepharospasm and for cervical dystonia. In the time to come, general diagnostic criteria for dystonia as a whole and specific criteria for focal dystonia syndromes will probably coexist. Clinical trials on focal dystonias require the harmonic implementation of well-defined criteria in multicentric settings. A currently unmet need is the characterization of clinical subtypes of dystonias and the identification of diagnostic criteria for each of them (**Figure 2**).

Based on current knowledge, it remains hard to accept dystonia as a single disease: nosologically, it is a collection

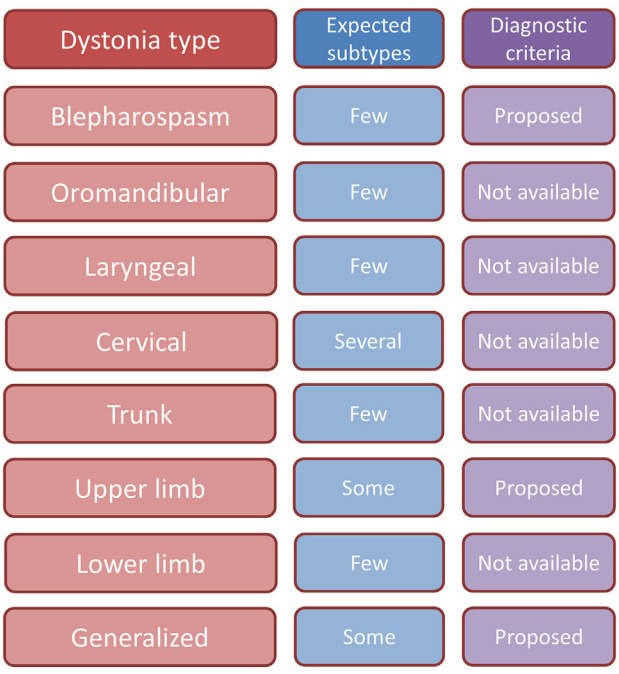

FIGURE 2 | Synopsis table of expected clinical subtypes and status of proposed diagnostic criteria for different dystonias.

of syndromes (93); phenomenologically, it is a collection of physical signs (85). However, there is no combination of physical signs that accommodates for all focal and generalized dystonia types: cranial and laryngeal dystonia have evidently a different phenomenology from limb and trunk dystonia. The physical signs of dystonia may apply to cervical and limb dystonia syndromes and may be used for the purpose of clinical diagnosis. By contrast, specific sets of clinical features and related diagnostic criteria still need to be developed for cranial and laryngeal dystonias.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Unmet Needs in Dystonia: Genetics and Molecular Biology—How Many Dystonias?

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Genetic findings of the past years have provided ample evidence for a substantial etiologic heterogeneity of dystonic syndromes. While an increasing number of genes are being identified for Mendelian forms of isolated and combined dystonias using classical genetic mapping and whole-exome sequencing techniques, their precise role in the molecular pathogenesis is still largely unknown. Also, the role of genetic risk factors in the etiology of sporadic dystonias is still enigmatic. Only the systematic ascertainment and precise clinical characterization of very large cohorts with dystonia, combined with systematic genetic studies, will be able to unravel the complex network of factors that determine disease risk and phenotypic expression.

Keywords: dystonia, genetics, GWAS, whole-exome sequencing, variant validation

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INTRODUCTION

Compared to many other neurologic diseases, the dystonias have only relatively recently been recognized as a group of somatic disorders with a characteristic spectrum of clinical manifestations and pathophysiological features. Although disturbed signaling of basal ganglia circuits have soon been identified as the major neurophysiologic substrate, in the absence of visible pathology on autopsy, the cause of what then was called "primary" dystonia, be it focal or generalized, with or without additional neurologic abnormalities, remained completely enigmatic. It was only the discovery of the torsinA (*TOR1A*) gene in 1997 (1) as the major cause for primary generalized dystonia, traditionally also called "Oppenheim's dystonia," that promised to shed more light on the molecular events leading to dystonic syndromes, and thus, the ultimate cause of at least a subgroup of dystonic disorders. Yet, despite the considerable progress that has been made in the years since this seminal discovery in the dissection of the genetic basis of dystonia, in the elucidation of molecular pathways and the development of animal models, it must be admitted that the path from mutation to disease is still poorly, if at all, understood, and thus, interventions based on a deeper understanding of the molecular pathophysiology of the dystonias are still lacking.

In the absence of this understanding, genotype–phenotype correlations were expected to help to understand the relationship between the molecular and clinical sphere by describing a more or less unequivocal clinical presentation to be associated with, and causally related to a specific genetic variant or mutation. While this has been relatively easy for DYT1-dystonia, with TOR1A mutations causing a rather specific phenotype of early-onset primary generalized dystonia with limb involvement, or in DYT11, the form of myoclonus-dystonia (M-D) caused by mutations in the *SGCE* gene (2), it has become clear that in most other cases, genotype–phenotype correlations

are much more variable and complex than initially believed and that genetic classifications do not translate one to one to clinical phenotypes. Mutations in some dystonia genes, such as *THAP1* (DYT6), can cause both focal/segmental and generalized forms of the disease, while others (e.g., TH or GCH1) may even give rise to both isolated and combined dystonias (3). The new classification of dystonias proposed by Albanese et al. takes these issues into account by clearly separating two "axes" of classification, i.e., clinical phenotype and etiology (4).

In addition, the vast majority of patients with the more common forms of dystonia, such as cervical dystonia, blepharospasm, or writer's cramp, have no or only an uninformative family history without clear Mendelian inheritance pattern. Moreover, issues including non-penetrance and variable expression of mutations even further complicates the distinction between complex and heritable forms of dystonia and will be discussed at the end of this chapter. Thus, the role of genetic factors in the etiology of these forms is still unclear, which has great impact on genetic counseling of patients and relatives. Nevertheless, the recognition of a small group of patients in whom a dystonia syndrome clearly is inherited as a monogenic trait (**Table 1**) allowed first "genetic entry points" and is beginning to give insight into the molecular pathogenesis of the disorder.

NOVEL GENES AND GENETIC RISK FACTORS FOR DYSTONIAS

The genetic analysis of the dystonias presents a number of challenges. At first glance, the presence of a genetic mutation seems to be an undisputable and objective finding in a patient with a familial neurologic disease. On closer inspection, however, the causative role of DNA-sequence variants of a given gene is often not easy to elucidate. This is why today the more neutral term "genetic variant" is often preferred to the term "mutation," which carries the connotation of being "harmful." Today it is clear that by far not all genetic variants, even in a gene known to be linked to a specific inherited disease, are in fact disease causing. Many cases with familial dystonia and the vast majority of sporadic cases cannot be explained by one or multiple presently recognized and validated mutations in known dystonia genes. Two technologies are promising to rapidly fill this knowledge gap: (i) whole-exome sequencing (WES) and (ii) genome-wide association studies (GWAS). While GWAS are designed to detect common (>5% in the population) genetic variants that usually reside in non-coding (presumably regulatory) regions of the genome and exert only a relatively small effect on disease risk, WES targets (usually rare) coding variants that are more likely to have a damaging effect on protein function.

WES in Dystonia

The part of the human genome that codes for proteins, the coding sequence (also called the "exome," as it is the sum of all exons), spans about 50 million base pairs. It contains several million rare to very rare variants from the consensus sequence, about 20,000 in any given individual. More than half of them lead to an alteration in the amino acid sequence of the encoded proteins (5), and thus can potentially change protein function. A comprehensive cataloging of these variants and the elucidation of their

TABLE 1 | List of genes for monogenic forms of isolated and combined dystonias.

Locus	Disease	Type	Inh.	Gene name	Chrom.
DYT1	Oppenheim's torsion dystonia	ID	AD	*TorsinA*	9q34
DYT2	Early-onset recessive TD	ID	AR	*HPCL*	1p35
DYT3	Lubag (x-linked dystonia-parkinsonism)	CD	X-R	*TAF1*	Xq13.1
DYT4	Whispering dystonia (one family only)	ID	AD	*TUBB4*	–
DYT5a/b	Dopa-responsive dystonia	CD	AD	*GCH1*, *TH*, *SPR*	14q22.1
DYT6	Craniocervical dystonia (Mennonite/Amish)	ID	AD	*THAP1*	8q21-q22
DYT7	Familial torticollis	ID	AD	–	18p
DYT8	Paroxysmal non-kinesigenic choreoathetosis	ID/CD	AD	*MR1*	2q33-q35
DYT9	Paroxysmal dyskinesias with spasticity	CD	AD	*GLUT1* (*SLC2A1*)	1p21
DYT10	Paroxysmal kinesigenic dyskinesia	ID/CD	AD	*PRRT2*	16p11.2
DYT11	Myoclonus-dystonia	CD	AD	*e-SG*	7q21.3
DYT12	Rapid-onset dystonia-Parkinsonism	CD	AD	*ATP1A3*	19q13
DYT13	Craniocervico brachial	ID	AD	–	1p36
DYT15	Myoclonus-dystonia	CD	AD	–	18p11
DYT16	Dystonia-Parkinsonism	CD	AR	*PRKRA*	2q31.2
DYT17	Juvenile-onset TD with torticollis and dysarthria	CD	AR	–	20p11
DYT18	Paroxysmal exercise-induced dystonia	ID/CD	AD	*GLUT1* (*SLC2A1*)	1p31
DYT19	Paroxysmal kinesigenic dystonia 2	ID/CD	AD	–	16q13
DYT20	Paroxysmal non-kinesigenic dystonia 2	ID/CD	AD	–	2q31
DYT21	Pure dystonia, mixed distribution	ID	AD	–	2q14
DYT23	Cervical dystonia/myoclonus-dystonia	ID	AD	*CACNA1B*	9q34
DYT24	Mixed dystonia	ID	AD	*ANO3*	11p14
DYT25	Cervical dystonia	ID	AD	*GNAL*	18p11
DYT26	Myoclonic dystonia	CD	AD	*KCTD17*	22q12
DYT27	Cervical/limb/generalized	ID	AR	*COL6A3*	2q37
	Cervical dystonia	ID	AD	*CIZ1*	9q34

Inh., inheritance mode; Chrom., chromosomal region.

The assignment of a DYT number does not mean that the pathogenic role of mutations in the listed genes is unequivocally confirmed.

functional consequences is a daunting task. Their low frequency (usually <1% in the population, often much lower) requires the study of very large patient cohorts, and the fact that their effect strength is likely to be only moderate (in other words, their penetrance on any phenotypic readout is incomplete) means that they can be also detected, although at even lower frequencies, in asymptomatic individuals. Also, the occurrence and frequency of those rare variants varies considerably between populations. This means that rare-variant association testing have to be done using carefully matched patient/control cohorts. Finally, it is very likely that interaction within functional gene networks plays an important role in determining overall function, a level of complexity that has not yet been addressed in most cases. Sophisticated bioinformatics analyses taking into account all these aspects will be necessary to make sense of the enormous amounts of data generated by WES.

The question of how to validate a potentially pathogenic mutation is of course not restricted to the dystonias or to inherited neurologic diseases. Guidelines have been published to establish a standardized workflow to assess the causal role of detected variants (6), but the issue remains challenging and many variants will have to be classified as "of unknown significance." Four lines of evidence can support a pathogenic role of a detected variant of which each has its merits and its limitations.

(1) Genetic evidence: co-segregation in a large family with demonstration of the variant in multiple affected and its absence in unaffected family members remains the most stringent proof of pathogenicity. Unfortunately, sufficiently large families are rare, and reduced penetrance or non-genetic phenocopies may hamper these analyses. Alternatively, a statistically significant enrichment of the variant in question in multiple patient cohorts as compared to unaffected controls may serve as genetic evidence for pathogenicity. Very large cohorts may be necessary to reliably assess the role of rare or very rare variants (with population frequencies of $\ll$0.1%).
(2) Population evidence: the frequency of an increasing number of genetic variants in the population is publicly available in a number of databases, such as the exome variant server (EVS[1]) or the ExAC database.[2] It is generally assumed that variants that are found at a relatively high frequency in such databases (e.g., >0.1%) are unlikely to be disease causing with high penetrance in rare diseases, because this would be incompatible with the epidemiology of these disorders. The limitation of these databases however is that they are derived from a collection of genetic exome sequencing studies, i.e., from patient cohorts with different diseases and from different countries. This clinical and demographic information is usually not available to users of the database, thus introducing unknown biases.
(3) *In silico* analysis: freely accessible computer programs have been developed to assess the functional consequences of DNA variation, such as PolyPhen[3] or SIFT[4] or mutation taster.[5] They are usually based on the analysis of phylogenetic conservation (assuming that a change of a highly conserved amino acid is more likely to be deleterious than more evolutionarily variable ones) or on the predicted biophysical consequences of an amino acid exchange. While those programs are of value, they are best used to provide guidance for further studies, rather than to use them to assign a pathogenetic role to a variant in the setting of clinical testing, because their reliability is still in question.
(4) Functional analyses: functional analyses in cellular or animal models can provide insight into the consequences of a coding mutation of a gene and can even allow to identify drug targets and promising lead compounds for correcting the dysfunction caused by a mutation. A good example is the electrophysiological analysis of mutations in ion channel genes using patch clamp techniques in the Xenopus oocyte system. However, in the majority of cases, the relevant cellular function of a gene product is unknown, and thus, it is also unclear if the readout in an artificial model system is relevant to the disease under question. The generation of transgenic mouse models used to be a time-consuming and costly procedure; however, the availability of the clustered regularly interspaced short palindromic repeats (CRISPR)-associated RNA-guided endonuclease Cas9 (CRISPR-Cas9) technology opens up new avenues for genetic follow-up work as it allows for relatively rapid and efficient screening for loss of functional consequences (7). Furthermore, in addition to the generation of loss of function alleles, this technology can be used to introduce human mutations directly in the genome of mice creating mouse models mimicking human disease and multiple genes can be edited at the same time allowing studying gene–gene interactions.

So far, WES has already successfully facilitated the discovery of several new rare Mendelian dystonia genes (8). For example, the genes *GNAL* and *ANO3* have been identified using exome sequencing approaches in large families showing clear segregation of the mutation with the disease (9, 10). Potentially pathogenic variants in these genes have also been found in other, independent cohorts (11, 12), which are absent from public exome databases, and electrophysiological studies suggested plausible functional changes in ion channel and second messenger function, thus fulfilling all the criteria for pathogenicity, as described above. However, the recent findings highlight the challenge for future research with the notion that several of the recently reported genes, e.g., *CIZ1* and *COL6A*, found in families with autosomal dominant and recessive isolated dystonia with cervical predominance, respectively (13, 14), could not be unequivocally confirmed by other groups (15).

[1] http://evs.gs.washington.edu/EVS/.
[2] http://exac.broadinstitute.org/.
[3] http://genetics.bwh.harvard.edu/pph2/.
[4] http://sift.jcvi.org/.
[5] http://www.mutationtaster.org/.

GWAS in Dystonia

While exome sequencing aims to identify rare variants thought to be disease causing in familial isolated or combined dystonias with moderate to high penetrance, GWAS are beginning to explore the role of common genetic variability as risk factors for sporadic dystonia. Most common variants are located not in the coding region of the genome, the exome, but rather in non-coding intronic or intergenic regions, or in 3′- or 5′-untranslated regions of genes. They do not alter the protein sequence, but rather are thought, if they are functional, to modify the expression, the regulation, or the use of alternative splice variants of nearby (sometimes also far away) genes. Notably, this gene selection may be biased for regions that contain multiple genes and have high linkage disequilibrium.

GWAS have been extremely successful in identifying dozens of risk loci for many neurologic diseases, such as Parkinson's disease, Alzheimer's disease, or multiple sclerosis (16–18). Usually, very large cohorts, in the range of thousands or tens of thousands of patients and controls, are needed to reliably detect these risk loci, because their individual effects are usually very small, increasing the risk to develop the disease under investigation by a factor of 1.1–1.5. Thus, this information cannot be used for individual genetic counseling, but rather is expected to provide insight into the molecular networks underlying the pathogenesis of complex disorders. So far, only relatively small GWAS have been undertaken in dystonic syndromes. Lohmann et al. decided on focusing on a very specific phenotype, musician's dystonia (MD), a form of the disease that affects 1–2% of professional musicians, speculating that this restriction would lead to a greater homogeneity of the patient sample and thus facilitate the detection of risk variants. They found common variants in the arylsulfatase G (*ARSG*) gene in a two-stage design, interrogating cohorts of 127 MD patients and 984 controls in the exploratory and 116 patients and 125 healthy musicians in the confirmation cohort (19). A single intronic variant was identified in an intron of *ARSG* (rs11655081; $P = 3.95 \times 10^{-9}$); odds ratio, 4.33; 95% confidence interval, 2.66–7.05. This variant was also associated with sporadic writer's cramp, a subtype of dystonia thought to be closely related to musician's dystonia ($P = 2.78 \times 10^{-2}$), but not with any other focal or segmental dystonia. ARSG hydrolyzes sulfate esters and is among others involved in protein degradation (20). The fact that dogs carrying homozygous mutations or dogs deficient for ARSG develop ceroid lipofuscinosis and accumulate heparin sulfate in visceral organs and central nervous system leading to behavioral deficits (21, 22) made ARSG an attractive disease gene for musician's dystonia. In an attempt to identify the causal mutation in *ARSG*, the coding region of *ARSG* was screened for mutations using Sanger sequencing in Dutch Writer's Cramp and German Musician's Cramp cohorts (23). Variant rs61999318 (p.Ile493Tyr) was significantly enriched in Writer's Cramp cases compared to European Americans in the EVS database ($P = 0.0013$), but no conclusive mutation was identified. Additionally, an overall enrichment for rare, protein-changing variants was observed in Writer's Cramp cases compared to controls ($P < 0.01$), validating a role of *ARSG* in Writer's Cramp.

In another GWAS, Mok et al. compared 212 cases with cervical dystonia with 5,173 controls (24). No single SNP was found to be associated on a genome-wide significance level (5×10^{-8}), but one variant was found to be suggestive near exon 1 of a gene for a sodium leak channel (*NALCN*) with a *P*-value of 9.76×10^{-7}. Dysfunction of such an ion channel is a plausible risk factor for dystonia, but in another small study, Gómez-Garre et al. were unable to confirm this association (25). The lack of association may be due to the fact that not all regions of the genome are equally covered, or that despite the large sample size there is lack of power to detect low effects, as is often the case for most associated or the associated gene identified by GWAS. In the end, only very large GWA studies including thousands of samples or large meta-analysis will be able to unequivocally resolve this issue.

EXAMPLE FOR PRIMARY GENERALIZED DYSTONIA (DYT1)

Primary generalized dystonia (Oppenheim's dystonia) is the prototype of a Mendelian form of the disease. It is most frequently, and possibly caused by a single specific mutation, a deletion of a single GAG triplet encoding a glutamate residue, in exon 5 of a gene, *TOR1A* (1), encoding an ATP-binding protein called TorsinA. The protein appears to have chaperone function and is located in the nuclear membrane and the endoplasmic reticulum, but its precise function is still unknown, and it is completely unclear why the loss of a glutamate residue, which is the result of the disease-causing GAG deletion mutation, leads to dystonia. Even in a relatively "simple" case such as DYT1-dystonia, there remain many unanswered questions with respect to genotype–phenotype correlations, for example, (i) what determines penetrance of the DYT1-mutation, i.e., why do some mutation carriers develop the clinically manifest disorder, while many others do not and (ii) can mutations other than the classic GAG deletion cause dystonia? The answer to both questions could provide important insight into the molecular events leading from mutation to disease.

Modifiers of the DYT1 Phenotype

Clinically, DYT1-dystonia presents almost always before the age of 20 years with an onset in a leg or arm, and progresses, not always, but in most cases, to a severe generalized form of the disorder (26). Remarkably, only about 30% of carriers of the disease-causing GAG deletion develop the disorder, suggesting the presence of genetic or non-genetic modifiers. Once the critical age is passed, a disease manifestation becomes unlikely, in contrast to neurodegenerative disorders. While reduced penetrance is the rule, rather than the exception in all neurogenetic disorders including DYT1-dystonia, its determinants are largely unknown, but can at least, in part, be explained by genetic modifiers. In addition, genetic modifiers may also account for differences in phenotypic expression of the GAG deletion leading to less common DYT1-dystonia phenotypes including late age of onset, focal, or segmental phenotypes and involvement of the craniocervical muscles (27).

One of such a genetic modifier variant involved in reduced penetrance is a relatively common coding polymorphism in the *DYT1* gene that affects nucleotide 646 of the cDNA sequence.

The respective codon encodes the amino acid aspartate (D) at position 216 of the protein (p.216D) (see **Figure 1**). About 85% of all chromosomes in a normal population carry the wild-type nucleotide guanosine, while approximately 15% of chromosomes carry the variant cytosine at this position, encoding the amino acid histidine (H). In itself, this polymorphism has no known functional consequence.

However, carriers of the rare histidine variant *in trans*, i.e., on the allele, which does not carry the disease-causing GAG deletion, appear to be protected from the deleterious consequences of the disease-causing mutation of the *TOR1A* gene. Risch et al. studied a cohort of manifesting and non-manifesting carriers of the GAG deletion and found that only about 3% of those with the H-allele will eventually show symptoms of dystonia, while penetrance is slightly increased, from 30% in all GAG deletion carriers, to 35% in those carrying the more common aspartate at position 216 (28). Obviously, this can explain only a small fraction of the total phenotypic variability, because the protective variant is relatively rare in the population, but it may serve as an example for other diseases and modifiers. A better understanding of this functional interaction could also provide interesting hints toward possible therapeutic targets.

Do Non-GAG Deletion Mutations in TOR1A Cause Dystonia?

The more widespread use of gene sequencing in dystonia patients has more recently uncovered a number of additional variants in *TOR1A* in patients with isolated dystonia. This poses the question if there is more than one genetic form of DYT1-dystonia. In a recent review, Dobričić et al. identified eight non-GAG deletion mutations in dystonia patients, most of them occurring in sporadic patients with adult onset forms of dystonia (29). This paper raises the important problem, how to validate the pathogenicity of rare variants detected by targeted or WES.

For *TOR1A*, for example, more than 100 rare variants are documented in the ExAC database, among them the p.Val129Ile change that was found in a patient with adult onset cervical dystonia by Dobričić et al. (29). While the prediction programs assigned the variant the status of "probably disease causing," and it was very rare in the ExAC database (9/121.412 alleles), genetic evidence from the family was not supportive (negative family history, three unaffected mutation carriers). Population data from matched cohorts with and without dystonia or functional assays are not available. Thus, the pathogenic role of this variant will remain uncertain, and the same is true for other variants in *TOR1A*.

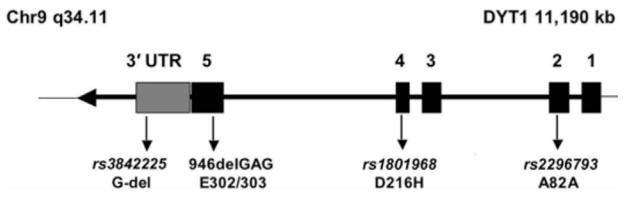

FIGURE 1 | Genomic structure of the *TOR1A* gene. The penetrance of the 946del GAG mutation in exon 5 (E302/303) is modified by polymorphism, rs1801968 (p.Asp216His). Reprinted from Ref. (28).

EXAMPLES OF COMBINED DYSTONIA (PREVIOUSLY "DYSTONIA-PLUS" SYNDROMES)

Dystonia may also co-occur with additional movement disorders such as Parkinsonism or myoclonus and are then referred to as M-D or dystonia with Parkinsonism (e.g., in dopamine-responsive dystonia). In exceptional cases, the dystonia is accompanied by other neurological or systemic disorders but these are beyond the scope of this article.

Mutations in *SGCE* Cause Myoclonus-Dystonia

Myoclonus-dystonia (M-D) is characterized by the combination of focal or segmental dystonia presented as cervical dystonia and/or writer's cramp and shock-like jerks most often affecting neck and upper limbs, whereas the legs are less affected. The myoclonic jerks can be significantly reduced by the consumption of alcohol. The onset of disease occurs most often in childhood but the symptoms can also present in early adulthood. The suggested prevalence of MD is about two per million in Europe (30). The disease is inherited in an autosomal dominant fashion and up to ~30% of the MD cases carry loss of function mutations in *SGCE* encoding epsilon sarcoglycan (DYT11) (2), indicating that not all *SGCE* mutations are identified using the current technologies and that additional MD genes can be found. The identification and functional characterization of these novel genes will increase our understanding of the underlying molecular biology of MD.

Genetic diagnostics of MD is sometimes complicated by the fact that *SCGE* undergoes maternal genomic imprinting, and markedly reduced penetrance is observed in affected families in which the mutant allele is silenced when inherited from the mother (31). Additionally, extended and complex MD phenotypes including cavernous cerebral malformations, hearing loss, and dysmorphisms may be the result of the fact that *SGCE* is sometimes deleted together with neighboring genes including *COL1A2* encoding the collagen alpha-2(1) chain reflecting haploinsufficiency of both *SGCE* and *COL1A2* (32). Patients with dominant negative mutations in *COL1A2* are linked to osteogenesis imperfecta types I–IV, Ehlers-Danlos syndrome type VIIB, recessive Ehlers-Danlos syndrome classical type, idiopathic osteoporosis, and atypical Marfan syndrome (33), whereas haploinsufficiency of *COL1A2* leads to milder phenotypes.

Novel Myoclonus-Dystonia Genes

In 2002, a second MD locus was mapped to chromosomal region 18p11 (DYT15) in a large Canadian family of whom all cases were affected by myoclonus and four also displayed limb-dystonia (34). Yet, up to date, this finding was not replicated nor was the disease gene identified. This further demonstrates the genetic heterogeneity of the dystonias. Additionally, given the notion that exome sequencing in linkage intervals is quite successful

suggests that either the mutation is missed due to (1) low coverage of DNA reads as, for example, the mutation may be present in a repeat-dense region, (2) the mutation is not covered by the exome capturing kit, or (3) the mutation is non-coding.

The successful combination of linkage analysis and exome sequencing was recently demonstrated by the identification of the disease genes for DYT23 and DYT26 (35, 36). In DYT23, a p.Arg1389His variant in *CACNA1B* encoding the voltage-gated calcium channel Cav2.2 was reported to cause MD plus in a large Dutch family. *Cacna1b* null mice exhibit a hyperkinetic movement disorder (37) and mutations in the homologous region of *CACNA1A* (Cav2.1), the subunit that together with Cav2.2 controls depolarization-induced calcium entry and transmitter release, were already reported to cause episodic ataxia and/or familial hemiplegic migraine (38). These findings support a role of Cav2.2 in the etiology of MD. Equally important, the p.Arg1389His variant fulfilled the majority of the four lines of evidence to support a pathogenic role. The variant (1) segregated in the family with the disease, (2) the MAF of the variant is <0.1% [carrier frequency of 0.0003809% in the EXAC browser (assessed January 2016)], (3) the variant was *in silico* predicted to be damaging, and (4) the variant affected channel functioning as was demonstrated by extensive electrophysiological studies in cell models. However, no second family carrying mutations in *CACNA1B* was yet identified and screening of an additional large European multicenter cohort of MD cases for the presence of the p.Arg1389His variant yielded identical frequencies in cases versus controls (39). Additionally, given that *CACNA1B* seems like the perfect candidate gene for this dystonia-plus syndrome, three other variants segregated with the disease in this family, the pathogenicity of the p.Arg1389His variant remains to be further confirmed *in vivo*.

In DYT26, two independent MD families of different ethnic background carried a recurrent mutation in *KCTD17* (p.Arg145His) encoding the potassium channel tetramerization domain containing 17 (36). This variant was not reported in ExAC, but variant p.Arg145Cys was observed with an allele frequency of 0.00001656. *KCTD17* was shown to operate in a large gene cluster involved in calcium-homeostasis and aberrant endoplasmatic reticulum calcium signaling was observed in fibroblast of patients. Both the genetic findings for DYT23 and DYT26 suggested alterations in calcium as pathomechanism underlying MD.

EXAMPLES OF DYSTONIA COMBINED WITH PARKINSONISM

Dopa-Responsive Dystonia

Dopa-responsive dystonia is characterized by a childhood onset dystonia with diurnal fluctuations (36). Importantly, the dystonia can be ameliorated by L-dopa treatment and Parkinsonism can occur later in the disease stage. Dopa-responsive dystonia also exhibits reduced penetrance, with unknown origin. Notably, the first disease gene that was identified to underlie a Mendelian form of dystonia was GTP cyclohydrolase (*GCHI*) (36). Mutations in *GCHI* led to autosomal dominant inherited dopa-responsive dystonia (DYT5a) and *GCHI* mutation carriers present with a childhood dystonia, but adult disease can mimic Parkinson's disease. Up to date, more than 100 different mutations have been identified throughout the coding region and 5′UTR region of *GCHI* and no clear genotype–phenotype correlation could be established. However, some of the mutations may predispose to the risk to develop Parkinson's disease (40). By sequencing, mutations in *GCHI* are found in only 40–60% of the dopa-responsive dystonias, leaving a large fraction of the patients genetically undiagnosed. GTP cyclohydrolase is involved in the production of an essential cofactor for biosynthesis of monoamine neurotransmitters, and additionally mutations in other enzymes leading to deficiency in the dopamine synthesis were reported to cause dopa-responsive dystonia, including tyrosine hydroxylase (*TH*), sepiapterin reductase (*SPR*), and 6-pyruvoyl tetrahydrobiopterin (*PTP*) synthase (41). Patients with mutations in these genes present with more severe and complex clinical pictures compared to heterozygous *GCHI* mutation carriers. Notably, cases with mutations in genes outside the dopamine synthesis pathway such as *ATXN3* causing spinocerebellar ataxia type 3 or SPG11 underlying spastic paraplegia type 11 can manifest as a dopa-responsive dystonia (42, 43), thereby broadening the clinical and genetic spectrum. With the introduction of exome sequencing in the clinic, novel disease genes underlying dopa-responsive dystonia will be identified.

Rapid-Onset Dystonia-Parkinsonism

Rapid-onset dystonia-Parkinsonism is characterized by a sudden onset of dystonia often accompanied with Parkinsonism within hours or weeks induced after mental stress or physical trauma. The disease is inherited in an autosomal dominant manner with reduced penetrance. Heterozygous missense and *de novo* mutations in the Na+/K+-ATPase alpha3 subunit (*ATP1A3*) can cause either rapid-onset dystonia-parkinsonism (DYT12) (44), or alternating hemiplegia of childhood (AHC), a severe neurodevelopmental syndrome characterized by hemiplegic episodes and neurological complaints (45), respectively. Notably, no *DYT12* mutations were reported to cause AHC, whereas in two cases the same amino acid was affected. In contrast, some AHC cases were reported to develop late-onset rapid-onset dystonia-Parkinsonism. Both *DYT12* and *AHC* mutations lead to reduced ATPase activity, whereas *AHC* mutations did not affect the protein expression level that was observed for *DYT12*. Recently, a third allelic disorder for *ATP1A3* was identified, episodic Cerebellar Ataxia, Areflexia, Optic Atrophy, and Sensorineural Hearing Loss (CAOS) by exome sequencing (45). How different mutations in *ATP1A3* can lead to three disorders with distinct neurological manifestations is not yet known and needs further functional investigations but highlights the complexity and challenges of current genetics research.

X-Linked Dystonia-Parkinsonism (Lubag)

X-linked dystonia-Parkinsonism (DYT3) is a recessive condition characterized by focal dystonia that is later followed by Parkinsonism. This rare condition is mainly prevalent in the Philippines and affects only males. Several disease-specific single-nucleotide changes (DSCs) and a small deletion were

detected within TAF1 RNA polymerase II, TATA box-binding protein-associated factor, 250 kDa (*TAF1*) (46). Makino et al. showed that some of these variants are associated with reduced neuron-specific TAFI expression (47) that may underlie altered expression of genes involved in vesicular transport and dopamine metabolism fitting well with the known molecular pathways involved in the etiology of dystonia. The question remains if *TAF1* is indeed the DYT3 disease gene and transgenic mouse models carrying the various genetic variations in *Taf1* are needed to answer this question.

DISCUSSION AND FUTURE PERSPECTIVES

While the abovementioned challenges of validating pathogenic variants and establishing robust genotype–phenotype correlations do not refute the validity of the original findings, it should stress the importance of replication of genetic findings. Particularly in the setting of genetic counseling of patients and their families, all genetic findings have to be treated with caution until unequivocal proof of pathogenicity is available. It is likely that over the coming years, dozens, maybe hundreds of genes, will be nominated as potential disease or risk genes for dystonia. Their functional validation will be a major challenge for neurology, genetics, and clinical neuroscience.

Despite these caveats, the identification of more genes causing different forms of dystonia will allow to construct an increasingly complex network of cellular pathways that promises not only to eventually provide a better understanding of the cause(s) of dystonia, hopefully leading to new and better treatments, but may help us to understand the functions of sensory motor integration of the human brain on a molecular level.

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DV and TG contributed equally to the writing of this review.

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REVIEW
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Blepharospasm: Update on Epidemiology, Clinical Aspects, and Pathophysiology

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Blepharospasm (BSP) is a rather distressing form of focal dystonia. Although many aspects of its pathophysiological mechanisms are already known, we lack fundamental evidence on etiology, prevention, and treatment. To advance in our knowledge, we need to review what is already known in various aspects of the disorder and use these bases to find future lines of interest. Some of the signs observed in BSP are cause, while others are consequence of the disorder. Non-motor symptoms and signs may be a cue for understanding better the disease. Various cerebral sites have been shown to be functionally abnormal in BSP, including the basal ganglia, the cortex, and the cerebellum. However, we still do not know if the dysfunction or structural change affecting these brain regions is cause or consequence of BSP. Further advances in neurophysiology and neuroimaging may eventually clarify the pathophysiological mechanisms implicated. In this manuscript, we aim to update what is known regarding epidemiology, clinical aspects, and pathophysiology of the disorder and speculate on the directions of research worth pursuing in the near future.

Keywords: blepharospasm, blink reflex, excitability testing, neuroimaging, epidemiology

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INTRODUCTION

Blepharospasm (BSP) is a form of focal dystonia that manifests with spasms of the eyelids, involuntary closure of the eye, and enhanced spontaneous blinking, or any combination of the previous ones. We have advanced in our knowledge of the disorders since the first descriptions of BSP as a form of dystonia (1, 2). However, there are still many unknown aspects in the generation of the disorder and unclear points in the pathophysiological mechanisms of the various forms of focal dystonia. BSP is particularly distressing. Patients may be functionally blind and unable to pursue a normal social life, with plenty of emotional and behavioral consequences. In this manuscript, we aim to update what is known regarding epidemiology, clinical aspects, and pathophysiology of the disorder and speculate on the directions of research worth pursuing in the near future.

REVIEW OF KNOWN BSP PHENOMENOLOGY

Epidemiology, Clinical Aspects, and Diagnostic Tools

Although BSP is now recognized as one of the most common forms of adult-onset dystonia, it is thought to be rare, affecting about 16–133 cases per million (3). By most studies, BSP seems to be less prevalent than primary cervical dystonia (CD) but in Japan, and in Italy too, the trend

is reversed, BSP being more frequent than CD (3). Peculiar characteristics of the BSP are female preference (3), peak age at onset between the fifth and the seventh decade, and a greater tendency to spread to adjacent body parts (usually within the first 5 years of history) than cervical and upper limb dystonia (4). BSP patients may also have tremor in the head or upper limbs (5).

Motor Phenomenology

Blepharospasm is characterized by stereotyped, bilateral, and synchronous spasms of the orbicularis oculi muscles. Spasms may be brief or sustained and may induce narrowing or closure of the eyelids. Other relevant manifestations include: sensory trick that can transiently improve eyelid spasms in about half of the patients (6), associated apraxia of eyelid opening (7), and increased spontaneous blink rate (8). Whether increased blinking may preceed BSP is an open question for future studies (9).

A diagnostic algorithm has been developed, based on motor manifestations of stereotyped, bilateral, and synchronous orbicularis oculi spasms, identification of sensory trick or, alternatively, increased blinking (5, 10, 11), which yielded 93% sensitivity and 90% specificity in distinguishing BSP from other conditions of involuntary lid closure such as eyelid tics, hemifacial spasms, facial chorea, apraxia of eyelid opening, frequent blinking, and lid ptosis due to myasthenia or other causes. The new severity scale was based on six clinical aspects, including degree and duration of eyelid closure, frequency of spasms, presence of apraxia of eyelid opening, occurrence of spasms during writing and increased blinking. The scale is suitable to assess BSP severity in clinical practice and research, yielding moderate to almost perfect reliability and acceptable clinimetric properties (5, 11).

Non-Motor Phenomenology

Several non-motor manifestations may be more frequent in BSP patients than in healthy or disease controls. They belong to four domains: sensory symptoms, psychiatric disorders, sleep disorders, and cognitive disturbances. Symptoms belonging to the sensory domain include burning sensation and grittiness in the eye, dry eye, and photophobia. Theoretically, eye symptoms may be part of the spectrum of BSP but they can also result from eye diseases of the anterior segment of the eyes, which have been identified with 77% sensitivity and 94% specificity in BSP patients (12).

Psychiatric alterations include depression, anxiety, and obsessive–compulsive disorders (13, 14). The finding is not specific because psychiatric disturbances, mostly depression, are also more frequent in patients with various forms of focal dystonia than in healthy controls. Theoretically, psychiatric disorders may be part of the clinical spectrum of the disease or secondary to the dystonia-induced disability. By most studies, depression appears to represent a feature of primary dystonia, whereas other psychiatric abnormalities have a less certain relationship and need additional evaluation.

Sleep impairment may be another feature of BSP (15). It seems to be independent of motor severity but rather correlated with depression. Therefore, it is not clear at present if there is a primary sleep abnormality in dystonia. Further studies are warranted.

There is little evidence of alteration of cognitive functions in idiopathic dystonia. Nevertheless, a recent study showed that non-depressed and non-demented patients with cranio-CD and normal IQ may have impairments in several specific cognitive domains including working memory, information processing speed, and set-shifting capacity (16). Altered cognitive measures were independent of the clinical expression of dystonia.

Neuroimaging

Structural

As in other forms of focal dystonia, BSP is considered to originate from a dysfunction in basal ganglia circuitry, although other brain and brainstem circuits can also be involved. Lesions causing BSP have been identified in various sites. In the analysis of their own cases, Khooshnoodi et al. (17) found 18 out of 1114 patients with BSP to have brain lesions that could account for their symptoms (1.6%). In a total of 48 cases (30 of them extracted from the literature), these authors reported lesions in several parts of the brain, including the thalamus in 12, lower brainstem in 11, basal ganglia in 9, cerebellum in 9, midbrain in 7, and cortex in 1. These observations have contributed to the idea of a widely distributed network of regions where lesions can potentially lead to BSP.

Although evidence for lesions in patients with BSP is scarce, researchers on brain neuroimaging have found group abnormalities in various sites also. The first to report on volumetric abnormalities in idiopathic focal dystonia was Black et al. (18). These authors studied 13 patients (5 with BSP and 8 with hand dystonia) and found that the gray-matter volume (GMV) of the putamen was about 10% larger in patients than in healthy controls. The authors speculated on the possibility that putaminal GMV change could be a response to dystonia if not related to its cause. A putaminal increase in GMV was confirmed in 16 patients with BSP by Etgen et al. (19) who used voxel-based morphometry rather than a direct analysis of a region of interest. These authors observed also decreased GMV in the left inferior parietal lobe, which correlated significantly with duration of botulinum toxin treatment and suggested a crucial role for the putamen in the pathophysiology of focal dystonia and secondary changes related with the tonic spasms and their botulinum toxin treatment for the left parietal region.

However, not all studies confirmed the increase in volume and hyperactivity in the striatal region. Obermann et al. (20) found a decrease rather than an increase in GMV in the putamen and thalamus bilaterally, whereas they reported increased GMV in the caudate head and the cerebellum, also bilaterally. In this study, though the authors examined patients with BSP (11) together with patients with CD (9) in an attempt to find common sites of involvement shared by these two forms of focal dystonia. In any case, they concluded that the morphometric changes found were located within structures important for sensorimotor integration and motor control, pointing out to a functional damage that, with time, may lead to structural changes. Other authors reported no significant change in microstructure of basal ganglia using diffusion tensor imaging (7) or voxel-based morphometry (21). The latter study is relevant for reporting, apart from the absence of changes in the basal ganglia, greater GMV in BSP

patients than in healthy volunteers in the right middle frontal gyrus and the reverse pattern (i.e., smaller GMV in patients than in healthy volunteers) in the left postcentral gyrus and left superior temporal gyrus. Therefore, these authors concluded that patients may have cortical but no basal ganglia changes. It is difficult to know the cause of the differences in the findings reported by Martino et al. (21) and those reported by Etgen et al. (19). Martino et al. (21) argued that the number of patients they studied was larger: 25 vs. 16 studied by Etgen et al. (19). However, it is difficult to believe that nine patients can account for the differences reported. Other factors have to be taken into account to explain the different findings reported so far, such as age at disease onset, disease duration, presence of dystonia spread to other body sites, dystonia severity, and duration and mean dose of botulinum toxin treatment. In none of these variables, the authors found a correlation with the neuroimaging findings but there can still be some influence from these variables enough to tilt the subtle abnormalities of BSP patients toward one or another direction.

Involvement of the cortex and the corticonuclear tract was supported by another morphometric study (22) that showed a significant decrease in GMV in the facial portion of the left primary motor cortex and right anterior cingulate of BSP patients when compared to healthy volunteers. An interesting comparison was made by Ramdhani et al. (23) between patients with task-specific (laryngeal dystonia and writer's cramp) and non-task specific (BSP and CD) forms of dystonia. They found that GMV changes in task-specific dystonia involved the brain regions responsible for sensorimotor control during writing and speaking, such as primary somatosensory cortex, middle frontal gyrus, superior/inferior temporal gyrus, middle/posterior cingulate cortex, and occipital cortex as well as the striatum and cerebellum (lobules VI–VIIa), whereas those in non-task-specific dystonia were limited to the left cerebellum (lobule VIIa) only. The authors concluded that these two forms of dystonia may have different pathophysiological mechanisms, may be precipitated by different triggers and express in neuroimaging as distinct microstructural patterns. The findings of Ramdhani et al. (23) are indeed stimulating for going further on structural and functional analysis of the brain in different forms of dystonia. They also put on show the contribution of the cerebellum as a key structure in the brain dystonia network (22, 24).

Indeed, the latest findings in neuroimaging studies have revealed microstructural abnormalities in the cerebellum. Yang et al. (25) studied diffusion tensor imaging and voxel-based fractal anisotropy in 9 patients with BSP alone, compared with 11 patients with BSP plus oromandibular dystonia. BSP patients showed significant FA reductions in the left anterior lobe of cerebellum that correlated negatively with disease severity, while patients with BSP and oromandibular dystonia showed an increase of FA in the right parietal lobe that correlated negatively with disease duration. Other abnormalities were also found in areas around the right precuneus, lentiform nucleus, and insula in different combinations in the two groups of patients. The authors concluded that white-matter changes outside the basal ganglia may present trait features that are specific for individual phenotypes of dystonia.

Functional

Many functional abnormalities have been reported in BSP patients. In 1995, Smith et al. (26) used [18F]fluorodeoxyglucose positron emission tomography (18-FDG PET) to find abnormally reduced medial frontal lobe glucose metabolism in four patients with apraxia of lid opening. A similar study on 10 patients with BSP showed increased glucose metabolism in the striatum and thalamus (27). Two interesting additional observations were made in that study: five patients were investigated before and after treatment of muscle spasms with botulinum toxin and showed similar results, indicating that the abnormalities were intrinsic of the disorder and not the consequence of increased muscle activity. On the other side, the authors did not find any significant correlation between severity of the spasms and the degree of striatum or thalamus hypermetabolism. Abnormalities in basal ganglia and frontal cortex have been reported since then, using various functional neuroimaging techniques, in various studies of patients with BSP (28). Kerrison et al. (29) reported cortical areas of increased glucose metabolism (inferior frontal gyri, right posterior cingulate gyrus, left middle occipital gyrus, fusiform gyrus of the right temporal lobe, and left anterior cingulate gyrus) and others with decreased glucose uptake (a region ventral to the area of increased glucose metabolism in the frontal inferior gyri). They also found increased glucose uptake in the right caudate and decreased glucose uptake in the left inferior cerebellar hemisphere and thalamus. Hutchinson et al. (30) examined PET in six BSP patients during sleep to avoid the possible confounding effect of spasm-related muscular contractions. They found that during sleep, patients showed frontal hypometabolism in a region associated with cortical control of eyelid movements while they showed hypermetabolism of the cerebellum and pons during wakefulness, when they exhibited involuntary muscle contractions. Apart from that, network analysis demonstrated overactivity of the lentiform nuclei, cerebellum, and the supplementary motor regions, reported by the same authors previously to be a pattern of abnormalities associated with other forms of dystonia. In a similar line of reasoning, Suzuki et al. (31) used also 18-FDG PET to investigate cerebral glucose metabolism in BSP patients whose spasms were suppressed by botulinum toxin injections. They found significant increase in glucose metabolism in the thalamus and pons that they interpreted as an expression of a compensatory change, common to pathophysiological mechanisms in other types of focal dystonia. The same authors have recently reported that the increase in putaminal glucose metabolism shown using 18-FDG PET in patients with essential BSP may separate them from those with drug-induced BSP who did not show such increase. A correlation between severity of the spasm and the intensity of increased glucose metabolism in the thalamus was reported by Murai et al. (32) in a study of a single patient who underwent five PET sessions during a follow-up of 22 months. An interesting approach was taken by Emoto et al. (33), who used 18-FDG PET to characterize photophobia in BSP patients. These authors found that patients with photophobia had significant hypermetabolism in the thalamus, while those without photophobia had significant hypometabolism in the superior colliculus. These findings may underlie mechanisms for the increase in the blinking rate in BSP patients with photophobia.

A functional magnetic resonance imaging (fMRI) study with analysis of the blood oxygenation level-dependent signal was done during spasms by Schmidt et al. (34). Healthy volunteers were asked to make a voluntary closing of their eyelids that was to be contrasted with rest, while patients were requested to press a button to mark the onset of their spasms. The authors reported on various areas activated with blinking, common to patients and healthy subjects, such as frontal and parietal operculum, supplementary motor area, primary sensorimotor cortex, various visual areas, and the cerebellum. The site where differences were observed was a subregion of the putamen, where the authors found hyperactivation in patients in comparison to healthy volunteers. Baker et al. (35) reported on the fMRI study of spontaneous and voluntary blinking in five BSP patients and five healthy subjects. The authors found greater activation in BSP patients than in control subjects in the anterior visual cortex, anterior cingulate cortex, primary motor cortex, central region of the thalamus, and superior cerebellum. Therefore, their findings suggested the existence of a hyperactive cortical circuit linking visual cortex, limbic system, supplementary motor cortex, cerebellum, and supranuclear motor pathways innervating the periorbital muscles. The existence of an abnormal default mode network implying the cortico-striato-pallido-thalamic loop has been suggested by Zhou et al. (36) after a fMRI study of resting state and voxel-based analysis of amplitude of low-frequency fluctuations.

Dopamine binding has been also examined in BSP. The first report was made in 1997 by Perlmutter et al. (37) who used PET to measure binding of radioligand [18F]spiperone in putamen in 21 patients and 13 healthy subjects to find decreased dopamine D2-like binding in 29% in dystonic patients. This was confirmed by Horie et al. (38), who found decreased binding in the entire striatal region (by a similar percentage in caudate and anterior and posterior putamen). The authors speculated on the possible mechanism relating dopamine ligand striatal deficit and decreased inhibition in BSP, typical of all forms of dystonia.

Neurophysiology

Dystonia is a functional disorder, and therefore, neurophysiology is a key methodology for its study, both for recognizing the underlying pathophysiological mechanisms and providing cues for the differential diagnosis when clinical signs and symptoms are not sufficiently clear. In the case of BSP, the most useful neurophysiological test is the blink reflex, which can be used to examine the excitability of brainstem interneurons, modulated in turn by circuits feeding on basal ganglia output signals (39–41).

Electromyography

The paradigmatic feature of dystonia is cocontraction between antagonistic muscles in attempts to perform a discrete movement. Therefore, one of the key methods for the documentation of abnormalities requires electromyographic recording of antagonistic muscles. This is not feasible in the muscles controlling the eyelid, the levator palpebrae, being unavailable to non-invasive electromyography recordings. A few authors have recorded from the levator palpebrae with needle electrodes showing the expected reduction of reciprocal inhibition (42, 43).

Simple observation of spontaneous blinking allows determining the rate of spontaneous blinking and the strength and duration of eye closure, measures that are rather useful for the characterization of BSP. Additional information can be obtained by recording the EMG activity from the orbicularis oculi with a pair of electrodes attached over the skin overlying the muscle at the lower eyelid. In healthy subjects, spontaneous blinking results from a brief phasic activation of the orbicularis oculi and relaxation of the levator palpebrae, but in BSP patients, the amount of EMG activity in the orbicularis oculi is usually markedly increased (41, 44, 45).

Blink Reflex

The study of reflex blinking is an important aspect of the evaluation of patients with neurological disorders. In the clinical context, gentle tapping of the forehead is the most common method to induce reflex blinking. If done repeatedly, clinicians are able to assess the inhibitory control of the reflex (the Myerson's maneuver). A startling stimulus, whether auditory, visual, or somatosensory, elicits reflex blinking as a form of eye protection (41, 46). However, the method that has been mostly used for the assessment of reflex blinking is the electrical activation of the supraorbital nerve while recording the EMG responses of the orbicularis oculi (47), which is conventionally known as the blink reflex. The electrically induced trigemino-facial blink reflex consists of two separate components: an early ipsilateral R_1 and a late bilateral R_2. R_1 is a pontine reflex, while R_2 is relayed through a more complex route including the pons and lateral medulla. The fact that unilateral stimuli give rise to bilateral responses permits separate assessment of the afferent and the efferent arms of the reflex circuit. Additionally, the blink reflex can be used to examine various functions that are either integrated in, or mediated by, the brainstem. If no peripheral nerve lesions interfere with the recording, the study of blink reflex becomes a useful technique for the assessment of supranuclear control of brainstem interneuronal excitability (41).

The best-known method for the assessment of blink reflex excitability is the paired shock technique, which consists in applying pairs of supraorbital nerve stimuli of the same intensity (48). The first stimulus (conditioning) induces a transient change in the excitability of reflex circuits, and the second stimulus (test), delivered at varying inter-stimulus intervals with respect to the first, is used as the probe stimulus. The size of the response elicited by the test stimulus is expressed as a percentage of the response to the conditioning stimulus, and a *X*–*Y* graph of excitability recovery can be represented for all intervals tested (usually between 100 and 1000 ms). The R_2 response is usually completely abolished from 0 to 200–300 ms, then very slowly recovers, reaching about 30–50% at the 500 ms interval and 70–90% at the 1500 ms interval in healthy volunteers. Blink reflex excitability is assumed to be under the control of rostral structures, including the basal ganglia (39, 40) and is abnormally enhanced in patients with BSP, which shows as a shift to the left in the excitability recovery curve. The **Figure 1** shows the methods and results in a single case.

Blink reflex excitability enhancement is not specific for dystonia, and, therefore, the test cannot be used for the diagnosis, although the data obtained may reinforce clinical suspicion.

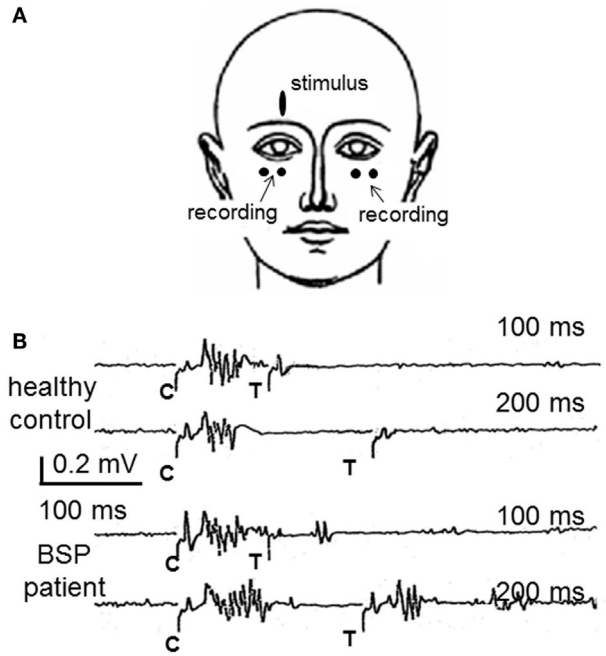

FIGURE 1 | The study of the blink reflex excitability recovery curve in blepharospasm. **(A)** The most frequently used method to examine patients with BSP is the recording of blink responses by surface electrodes attached over the orbicularis oculi muscles. **(B)** Partial results from a study of blink reflex excitability recovery in a healthy control and a BSP patient. Pair of supraorbital nerve stimuli are applied either 100 or 200 ms apart. The conditioning stimulus (C) elicits the typical blink reflex, composed by R_1 and R_2 responses. The test stimulus (T) elicits no R_2 response in the healthy control, which reflects the normal lack of excitability at such short intervals, whereas they elicit an R_2 response in the patient, larger with the interval of 200 ms, reflecting the enhanced blink reflex excitability, characteristic of BSP. Part **(A)** of this figure was previously published as part of Figure 19.6 of Ref. (45) and is reproduced with permission from Elsevier. Part **(B)** of this figure was previously published as Figure 1 in Valls-Sole's "Assessment of excitability in brainstem circuits mediating the blink reflex and the startle reaction," published in Ref. (41), and is reproduced with permission from Elsevier.

Interestingly, however, it has been reported normal in patients with psychogenic dystonia (49), which makes the test clinically very useful. In fact, blink reflex excitability depends on excitatory inputs reaching brainstem interneurons in the trigemino-facial pathway. One such input is a startling auditory stimulus (SAS). This generalized reflex response, and the more discrete auditory blink reflex, is mediated by the nuclei of the reticular formation. A regulatory step in the pathway is likely the pedunculopontine tegmental nucleus, which also receives inputs from the internal pallidum and other basal ganglia nuclei. The pedunculopontine nucleus has an inhibitory action on the startle blinking, and one way to document the inhibitory control of the blink reflex is prepulse inhibition (50, 51).

Prepulse inhibition is defined as the inhibitory effect of a stimulus (weak enough not to induce a reflex response by its own) on the response to another, suprathreshold, stimulus. This effect is considered to be due to the attentional shift required to process the information brought about by the prepulse. Prepulse inhibition has been found abnormal in patients with BSP, particularly in those who cannot find relief of their symptoms using a "geste antagonistique" (52). The abnormalities in prepulse inhibition show functional impairment of a circuit that is different from that of the blink reflex excitability recovery curve (53).

An animal model of BSP has been reported in which a 6-hidroxi-dopamine lesion of the striatum together with a peripheral nerve lesion may lead to enhanced reflex gain (54, 55). This may apply to humans with some predisposition to develop dystonia, where unilateral peripheral facial nerve lesions lead to enhancement of blink reflex excitability recovery in the side contralateral to paresis. That such changes in the contralateral facial nerve are related to the afferent input from the cornea of the paralyzed side was first suggested by Chuke et al. (56), who found that the BSP-like sustained contraction of the facial muscles of the side contralateral to the paralysis was relieved by helping to close the eye with a weight added to the paralyzed eyelid. Further evidence in the same direction was reported by Manca et al. (57), who analyzed the size differences between the responses recorded in the non-paralyzed side to ipsi- and contralateral supraorbital nerve electrical stimulation. These are examples of maladaptive plastic changes in the control of brainstem excitability that, in predisposed subjects, may lead to clinical expression of dystonia.

Other Neurophysiology-Based Recordings

Little information exists on direct neurophysiological recordings from the structures supposedly dysfunctional in BSP, i.e., the basal ganglia, thalamus, brainstem, or cerebellum. Deep brain stimulation (DBS) has been used scarcely to treat BSP patients because significant symptomatic alleviation is usually provided by injections of botulinum toxin in the orbicularis oculi muscles. The few reports published on DBS in BSP patients (actually in patients combining BSP and oromandibular dystonia) deal with clinical and epidemiological aspects (58–60). Special mention should be given to the report of a single patient by Foote et al. (61). In this case, the authors reported an increase in single cells firing rates in the GPi of the right side, which may relate to the hyperactivity reported with neuroimaging studies. An interesting aspect is that the firing rate was less increased in the left side, operated 6 months after the right side, indicating effect of DBS beyond the site of implantation. DBS may not always be beneficial but sometimes may worsen symptoms in BSP patients (62).

The blink reflex can be elicited not only by trigeminal stimuli but also by other somatosensory stimuli applied elsewhere in the body, the so-called somatosensory blink reflex (63). This type of reflex has been also reported to show an abnormal excitability enhancement in patients with BSP (64), which challenges the hypothesis of the influence of the basal ganglia over trigeminal neuronal excitability as the cause of the alterations of the blink reflex in BSP, unless we assume that the somatosensory inputs use common interneurons to the trigemino-facial pathway for the elicitation of the blink reflex. An auditory stimulus elicits also a blink reflex and this has been found exaggerated in BSP patients (65). These authors recorded auditory startle responses (ASRs) from masseter, orbicularis oculi, sternocleidomastoid,

and biceps brachii muscles and found abnormalities of different types (shortening latency, increased response probability, or enhanced response size in various of these muscles), pointing out to a general increase of response excitability to the auditory stimuli.

Patients with BSP have shown increased levels of activity in the orbicularis oculi in comparison to healthy subjects (66). One of the reasons for such increase in activity may be the visual stimuli acting on reflex contraction. Light is undoubtedly a source of discomfort in patients with BSP and, consequently, reduced eyelid contraction force has been reported together with increased comfort and reduction of overall light sensitivity and BSP frequency in patients with BSP using FL-41 tinted lenses (67).

HYPOTHESES FOR FUTURE WORK

Many lines of research are of interest for further understanding the pathophysiological mechanisms of BSP. Various of them have been suggested along the previous paragraphs. In neuroimaging, it is apparent the shift of interest, driven out of building hypothesis on experience, from early sites of secondary dystonias in the basal ganglia through the involvement of the parietal cortex and the thalamus to the most recent hint on the cerebellar dysfunction. Certainly, all these structures may form a network that is dysfunctional in BSP, but the exact contribution of each and the overall cause of the dysfunction are still unknown. Tools to study cerebellar function in relation to the eyelid movements or orbicularis oculi contraction are very scarce. Recently, though, Ryan and coworkers (68) have suggested that eyelid conditioning and long-term depression of the blink reflex induced by a high frequency electrical discharge on the trigeminal nerve before elicitation of the blink reflex may share the same circuits and suggested that such high frequency stimulation may be a way to long-term depress trigeminal blink circuit activity in diseases like BSP. In fact, studies of eyeblink conditioning in BSP have not been reported so far, probably because of the difficulties related to interference by involuntary spasms.

An area deserving more study in BSP is the relationship between the antagonistic muscles in control of eyelid position. The orbicularis oculi muscle is easily accessible with surface EMG but the levator palpebrae muscle requires needle recording and the recording system itself is nowadays undoubtedly interfering with normal behavior. Eyelid position is controlled involuntarily by many sources, including the amount of light, tiredness, emotion, pain, and many other inputs. Likely, the levator palpebrae is tonically active most of the time, requiring some phasic contribution from the orbicularis oculi to refresh or reset the activity. A premovement silence of the tonic activity of the levator palpebrae may be needed for this muscle to have a burst of activity large enough to elevate the eyelid. The orbicularis oculi spasms may just be the result of unsuccessful attempts to reset the levator palpebrae, much as it has been described for the soleus when a standing person prepares for fast tip-toeing in a reaction time ask paradigm (69). How these mechanisms apply to BP is not yet fully understood but the fairly intimate relationship between the two muscles is certainly impaired in these patients.

Finally, another area in which research must be much rewarding for the care of BSP patients is the understanding of the role of eye diseases in the generation of BSP. A significant positive association between BSP and prior eye diseases has been reported by Defazio et al. (70). Symptoms of dry eye and other alterations are common in these patients but we do not know if they are consequent to, causative of, or concomitant with, BSP. Noxious stimuli may trigger reactions that are out of our conscious control. Awareness of them is not always easy and sensitization of circuits may take place even before the patient realizes that something is wrong. If we accept that this is one mechanism for the generation of BSP, we need early detection of possible eye disorders causing abnormal sensation or involuntary reactions to look for means to avoid consolidation of potentially abnormal circuits in case the disorder does not have a solution.

CONCLUSION

There is much work to do to understand and treat BSP, ranging from muscle dysfunction to cerebral abnormalities. We do not know if some signs observed are cause or consequence of the disorder. The involuntary reaction of the body to a relatively small insult may modify circuits that later would lead to the complexity of symptoms characteristic of the disorder. We have to recognize the noxious stimulus that first triggered the process and separate it from the complex reactions leading to adaptation and compensation that finally lead to dystonia. The study of phenomenology can quantify and document the clinical expression of the disorder but this is not sufficient. Serious cooperation among various specialties is a must for the ophthalmologists to treat eye disorders, neurologists to detect early signs of abnormal behavior, psychologists to take care of emotional and cognitive disorders, rehabilitation experts to help generate beneficial plastic changes, and others.

AUTHOR CONTRIBUTIONS

JV-S and GD have contributed equally to the completion of this manuscript. Both have met and discussed on how to prepare the review. GD was more in charge of clinical and epidemiological aspects, while JV-S was more in charge of neurophysiology and neuroimaging.

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Unmet Needs in the Management of Cervical Dystonia

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Cervical dystonia (CD) is a movement disorder which affects daily living of many patients. In clinical practice, several unmet treatment needs remain open. This article focuses on the four main aspects of treatment. We describe existing and emerging treatment approaches for CD, including botulinum toxin injections, surgical therapy, management of non-motor symptoms, and rehabilitation strategies. The unsolved issues regarding each of these treatments are identified and discussed, and possible future approaches and research lines are proposed.

Keywords: cervical dystonia, botulinum toxin, deep brain stimulation, physical therapy modalities, non-motor features

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INTRODUCTION

Cervical dystonia (CD) is the most prevalent form of adult-onset focal dystonia, and is characterized by abnormal postures of head and neck, that can considerably impair daily living.

There are several unmet needs in the management of CD. In this article, we focused on four main aspects of the treatment of this disorder, including botulinum toxin injections, surgical therapy, management of non-motor symptoms (NMS), and rehabilitation strategies.

For each of these issues the state-of-the art is presented and some of the current knowledge gaps are highlighted. In addition, we propose potential research lines that could be developed to manage these issues.

BOTULINUM TOXIN

What Is Known?

Botulinum neurotoxin (BoNT) injections are the treatment of choice for CD.

There is class I evidence to support efficacy and safety of the three commercially available formulations of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) (1–3), and of BoNT-B (rimabotulinumtoxin B) (4).

As much as 70–85% of the patients report a significant benefit from the treatment (5). Efficacy on motor symptoms varies from 20 to 70%, based on the assessing method used. Significant improvement is also documented on pain and quality of life (QoL) (6).

Although BoNT treatment is routinely performed worldwide and is satisfying for many patients, the obtained effect is still far from optimal. In addition, BoNT treatment is in some cases associated with the occurrence of side effects, such as dysphagia or excessive muscle weakness. These side effects

are due to an excessive dose of BoNT or to the spread of BoNT to adjacent structures, and may limit the efficacy of the treatment.

What Is Uncertain?

In order to further improve the efficacy and safety of the treatment, the accurate placement of the minimum effective dose of toxin in the dystonic muscles should be ensured. At present, there is still no agreement on a recommended starting dose or on the minimum effective dose per muscle.

Moreover, there is still great variability concerning treatment strategies. Multi-point BoNT injections have been proposed as more effective than single point injections (7), but convincing evidence on these topics is still lacking.

The use of polymyography to identify dystonic muscles before treatment, and the use of electromyography (EMG) to guide injections, has been proposed to improve the accuracy of BoNT delivery. While some studies show that this approach may provide a significant advantage in BoNT-naïve patients (8, 9), as well as in patients unsatisfactorily treated with standard injections (10, 11), this still need to be further confirmed in larger series. Moreover, the modalities and indications of the neurophysiological approach need to be further specified.

The use of imaging techniques has also been proposed to identify the dystonic muscles before treatment and to improve the accuracy of the placement of BoNT. Preliminary reports suggest that the use of ultrasound-guided injections might help localizing the target muscles and reducing the episodes of dysphagia in patients who had experienced it with standard treatment (12).

A number of patients do not respond to BoNT treatment, or develop a secondary resistance. A currently accepted definition of secondary non-responsiveness implies "insufficiently improved posture after three or more unsuccessful injection cycles in CD patient's previously achieving satisfactory results" (13).

Change in CD pattern across time, with the appearance of more complex multiaxial dystonic movements or tremor, account for some of the non-responders. Another well-known cause of non-responsiveness is the development of antibodies against BoNT formulations (14). This issue has been described with different BoNT formulations, including onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB (15), while it does not seem to be a concern when incobotulinumtoxinA is used (16). At present, there is no agreement on the strategies to avoid the formation of antibodies. Although this problem likely occurs only sporadically, a minimum safe interval of 12 weeks or longer is still used in most centers (17). This strategy, however, limits treatment of a larger number of patients, who report reemergence of symptoms before this time. The safety of shorter intervals between injections and of the so-called booster injections still needs to be explored.

Another unsolved and largely debated practical issue concerns the optimal conversion ratio between different formulation of BoNT-A, or between BoNT-A and BoNT-B.

Based on studies using different methodology, a conversion of onabotulinumtoxinA to abobotulinumtoxinA 1:3 IU (18, 19), as well as ratios of 1:2.5 (20) have been proposed over time, while a conversion ratio of 1:1 is proposed for onabotulinumtoxinA to incobotulinumtoxinA.

Future Perspectives

Future research lines should focus on improving the benefit/side effects ratio of BoNT treatment and on reducing the rate of primary and secondary non-responsive patients.

A standardized working definition of non-responsiveness should be developed, which should take into account an objective measure of the lack of improvement as well as an evaluation of the appropriateness of BoNT treatment. An objective and universally accepted working definition would be of crucial importance to assess new treatment strategies and to identify patients for whom more invasive (surgical) treatment are indicated.

Dose-finding studies and comparative studies across different toxins should be performed. The additional value of neurophysiology and imaging in improving the intramuscular placing of BoNT should be explored. In order to minimize patients' discomfort, the minimum safe interval between treatments should be determined.

SURGICAL TREATMENT

What Is Known?

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) is an established surgical treatment for patients with generalized dystonia (21, 22). Because the initial studies suggested an equally beneficial effect for all body regions, the method was soon applied to patients with focal or segmental dystonias, who no longer responded to BoNT.

Krauss was the first to describe the beneficial outcome in three patients with CD in 1999 (23). Meanwhile three controlled clinical studies were conducted evaluating GPi-DBS in CD patients who failed on medical treatment: a Canadian prospective, multicenter and observer-blinded study assessed 10 CD patients who were further followed for 12 months (24). Motor improvement was 28% at 6 months and 43% at 12 months (TWSTRS motor score). Pain and disability scores were also improved by 66 and 64%, as well as mood [Beck's Depression Inventory (BDI)] and QoL (SF-36) by 58 and 24%, respectively. Another prospective single-center study followed eight CD patients for up to 48 months after GPi-DBS (25), reporting a median reduction in the TWSTRS motor score of 50% at 6 months and of 73% at last follow-up. The only randomized sham-controlled multicenter study of bilateral GPi-DBS in CD followed patients for a total of 6–9 months after surgery (26). Sixty-two patients were implanted with a neurostimulation system and randomly assigned to either active or sham stimulation (stimulator output 0V). After 3 months, TWSTRS severity score was reduced by 26% in the treatment group compared to 6% in the sham group. There was a 3.8 point difference between both groups, which was significant. TWSTRS disability score and Bain tremor score were also significantly improved in the neurostimulation group, whereas TWSTRS pain score and QoL (Craniocervical Dystonia Questionnaire-24 score) were not different. Evaluations were repeated in all patients after receiving 6 months of effective neurostimulation. At the follow-up, significant improvements compared to the pre-surgical baseline were found for TWSTRS severity score (28%), disability score (46%) and pain (51%),

Tsui score (57%), Bain tremor score (66%), and global dystonia ratings by patients (49%) or physicians (53%). BDI was reduced by 20%, the cranio-cervical dystonia questionnaire-24 showed a 28% improvement. No permanent adverse effects were found. Transient adverse effects included device infection ($n = 3$), misplacement/dislocation of electrodes ($n = 3$) or neurostimulator ($n = 1$), stroke/hemorrhage ($n = 1$), and seizure ($n = 1$). Four patients claimed pain at the extension cable. The most frequent stimulation-induced side-effect was dysarthria (seven patients). Stimulation-induced bradykinesia was observed in one patient, but has previously been described as a relevant adverse effect of pallidal neurostimulation in several series (27, 28).

It has been suggested that the subthalamic nucleus could be a better target for DBS in CD with equal motor benefit but less risk of stimulation-induced parkinsonism (29).

What Is Uncertain?

Larger series are needed to ascertain which types of CD respond best to pallidal DBS, and to assess predisposing factors and the true prevalence and risk factors of stimulation-induced parkinsonism. Subthalamic stimulation, which was forwarded as an alternative, induces (transient) dyskinesia in a large proportion of patients and the cognitive and behavioral safety has not been evaluated yet. So far, DBS has been advocated only in patients no longer responding to BoNT treatment, as a last line therapy. A comparative trial of BoNT treatment in comparison to DBS has not been performed yet.

Future Perspectives

Registry data of DBS surgery in CD would help to evaluate outcomes in daily practice, define responder profiles, and assess the frequency of less common adverse effects. The effect of DBS on non-motor features should be systematically assessed. Randomized controlled trials (RCTs) are needed to compare pallidal and subthalamic neurostimulation and DBS in general vs. best conservative management of CD.

MANAGEMENT OF NON-MOTOR SYMPTOMS

What Is Known?

Growing evidence suggests that the phenotype of dystonia includes also NMS, which could in part account for the reduced QoL in CD (30, 31).

Sensory abnormalities are the most frequently NMS associated with CD. The onset of motor symptoms can be preceded by a feeling of discomfort in the neck and dystonic movements are sometimes interpreted as an attempt to decrease this feeling (32). Involvement of the sensory system is also indicated by the *geste antagoniste*, which modifies cortical EEG activity and GPi local field potentials, even before touching the head (33). Furthermore, several studies found abnormalities in temporal and spatial discrimination thresholds in CD patients, both in affected and unaffected body parts, and in unaffected first-degree relatives (34, 35).

Pain is present in up to 90% of CD patients, which is rated as moderate to severe by 70% (36). Two-third of the patients use analgesics. Pain might be a consequence of motor symptom severity (37), but could also be influenced by depressive and anxiety symptoms (31). It is proven that BoNT treatment as well as surgical treatments, such as DBS (26) or selective peripheral denervation (38), significantly improves pain associated with CD (36, 37).

The prevalence of psychiatric disorders in CD can reach up to 91.4%, compared to 35% in the general population (39). This could logically be the consequence of living with a chronic, visible, and invalidating disorder. However, compared to the prevalence of psychiatric symptoms in other chronic and visible diseases, such as alopecia areata, CD patients still have a significantly increased odds ratio to develop psychiatric co-morbidity (40). The most prevalent psychiatric disorders include depressive symptoms (40–45), anxiety symptoms/panic disorders (39, 40, 44, 45), obsessive–compulsive symptoms (41, 45) and substance abuse (45). Importantly, a few studies showed that psychiatric co-morbidity is the most important predictor of poorer health-related QoL, especially for the domains general health, role functioning, bodily pain, and emotional and mental health (31, 46, 47).

At this moment, no treatment trials have been described with the aim to directly improve psychiatric symptoms in CD patients.

What Is Uncertain?

The prevalence and characteristics of the different NMS in CD, including sleep disturbances and cognition, have not been systematically studied and existing studies show contrasting results. A recurring debate is whether NMS are a direct consequence of the motor symptoms of dystonia or intrinsic to the neurobiology and thereby part of the phenotype.

Cervical dystonia patients showed an impaired sleep quality compared to healthy controls: in two studies, this was correlated with depressive symptom scores (48, 49), while in one study it appeared to be independent from psychiatric disorders and medication use (50). Successful BoNT treatment did not improve sleep quality, arguing against a secondary discomfort due to the dystonia motor symptoms (50). Excessive daytime sleepiness was detected in one study, but at least in part explained by the use of anticholinergic drugs (51). Other studies did not find significant differences in daytime sleepiness (48, 49).

Studies concerning cognitive impairment in CD are still very limited. One study showed impairments in the domains working memory, processing speed, visual motor ability, and short-term memory (52). Other small studies found impairment of visuospatial function (53) and a sustained attention deficit, the latter disappearing after BoNT treatment (54).

Convincing data support a disruption of sensory-motor system also in healthy first-degree relatives of dystonic patients, suggesting a possible endophenotype (55). For example, temporal discrimination threshold (TDT) was found abnormal not only in about 80% of dystonia patients but also in about 50% of first-degree female relatives older than 48. In male relatives, the penetrance was reduced (34, 56).

The onset of psychiatric disorders before the onset of the movement disorder in ~70% of the cases (42, 44, 45) is one of

the strongest arguments toward a shared pathophysiology. This is also supported by a men-to-women ratio of psychiatric disorders of 1:1 in CD patients compared to 1:2 in the general population, higher incidence of psychiatric disorders in CD patients compared to other visible and chronic disorders, and different personality profiles found in CD patients, which develop long before adolescence and onset of motor symptoms (35).

Drawing firm conclusions on the etiology of NMS in CD remains difficult, also considering the tight correlation between pain, psychiatric symptoms, sleep disturbances, and motor symptoms.

Future Perspectives

In order to solve the issue of the etiology of NMS in CD, prospective studies are necessary. Selecting an appropriate group for prospective studies has proven challenging. This might change with the identification of genetic forms of CD, such as the *GNAL* and *ANO3* gene (57–60), which would allow studying homogeneous clinical subgroups, even in the pre-symptomatic phase.

Another strategy could be the identification of endophenotypes in larger groups, based on biomarker, such as the TDT.

Clinical trials are required toward the effect of treatment of NMS on health-related QoL.

REHABILITATION STRATEGIES

What Is Known?

Evidence toward the effectiveness of rehabilitation strategies is scarce. Two systematic reviews described the effects of different rehabilitation strategies in various forms of primary dystonia (61) and CD alone (62), suggesting that multimodal physical therapy (PT) programs, added to BoNT treatment, further improve disability and pain compared to BoNT treatment alone (61, 62). Only three clinical trials (63–65) and one case–control study (66) investigated the effects of a multimodal PT program in combination with BoNT treatment.

One single-blind RCT in 40 patients showed significant improvements on pain and daily-life activities, and a prolonged duration of the BoNT effect, after a 6-week PT program of active exercises, muscle stretching and massage compared to BoNT treatment alone (63). A second single-blind RCT in 40 patients showed decreased disability and a significant decrease of head deviation and improved hand functions after a 6-week PT program of active exercise, muscle stretching, and TENS in addition to BoNT treatment (64). The third single-blind RCT of 20 patients found only a trend toward greater improvement on head posture, pain, and disability in the group that received 12 weeks of active exercise, relaxation, and BoNT treatment compared to the group that received relaxation and BoNT treatment only (65).

One case–control study followed 40 patients in a 4-week PT program of active exercise, muscle stretching, active and passive neck mobilizations, and electrostimulation of the dystonic muscles in adjunction to BoNT treatment, or BoNT treatment alone. The PT group showed significantly more improvement on pain, and on some subscales of the SF-36 (66).

What Is Uncertain?

The available results should be interpreted with caution. The content of PT programs varied across studies, including motor learning exercises [Bleton method (67)], passive or active mobilization techniques of the cervical spine, stretching of the dystonic muscles, relaxation, and electrotherapy, such as EMG biofeedback or TENS. It is, therefore, difficult to identify the most effective intervention or combination of interventions.

Frequency and duration of PT sessions also varied from 40 min every other day for 6 weeks (64), 75 min 5 days a week for 5 weeks (66), 90 min a day for 2 weeks (63) up to a 12-week program with a weekly 30-min session during the first 4-weeks, and a session every fortnight for the remaining 8 weeks (65). Besides, current studies mainly show short-term effects associated with brief and intensive PT programs (63, 64, 66), which could be difficult to implement in current regular care of a chronic disease, such as CD. The long-term effects of less intense and longer PT programs have not been explored yet.

Future Perspectives

Future research should focus on standardized PT programs that are effective but also adequate to treat patients with a chronic conditions and an active life. PT programs with longer treatment periods and the emphasis on self-management of symptoms and the ability of patients to improve their performance of daily life tasks should be the focus. Currently, such a PT program is being investigated in a large Dutch RCT (68).

The effect of PT interventions on the pathophysiological mechanisms of CD should also be studied. Although the pathophysiology of CD remains largely unclear, maladaptive neuroplastic changes may play an important role (69). By integrating PT programs with modern training principles that have proven relevant for neural rehabilitation and motor learning, these deficit may be altered (70–74).

Additionally, high-quality research combining electrophysiological parameters or imaging techniques with clinical outcomes can help to further unravel the effects of PT programs on CD.

FINAL CONSIDERATIONS

There are still many unmet needs in the management of CD. A better understanding of the pathophysiology of CD is necessary to plan new treatment strategies and to improve existing treatments. In addition, the available rating scales for CD have some clinimetric issues and do not equally address all the domains of the disease. This points to a need for updated scoring instruments in order to support studies on the pathogenesis and progression of the disease and to more accurately evaluate the outcomes of clinical trials. Specific standardized rating scale for NMS in (cervical) dystonia should also be developed.

Finally, it is widely accepted that motor improvement is not the only determinant of treatment success in CD: pain, social distress, and psychological factors play sometimes a greater role toward patient satisfaction. This calls for a multi-disciplinary approach posing more attention to the subjective determinants of QoL in CD.

AUTHOR CONTRIBUTIONS

All the authors (MC, MS, JD, JV, and MT) provided substantial contributions to the conception or design of the work; drafted part of the manuscript and revised the rest of the manuscript critically for important intellectual content; approved the final version to be published; agreed to be accountable for all aspects of the work.

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CORRECTION
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Corrigendum: Unmet Needs in the Management of Cervical Dystonia

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Keywords: cervical dystonia, botulinum toxin, deep brain stimulation, physical therapy modalities, non-motor features

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DESCRIPTION OF THE MISTAKE BEING FIXED

In the original article, we neglected to thank our sponsor, European Cooperation in Science and Technology (COST), Action BM1101 "European network for the study of dystonia syndromes." The authors apologize for this oversight.

This error does not change the scientific conclusions of the article in any way.

The correct text of the acknowledgments should read as below.

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Conflict of Interest Statement: MC, Advisory board: Medtronic, Boston Scientific, is co-inventor on a patent application relevant to Deep Brain Stimulation (2014). Speaking fees: Abbvie, Medtronic, Boston Scientific, ECMT. Grant: Stichting Parkinson Fonds. MS: Grants: University Medical Centre Groningen, Stichting Wetenschapsfonds Dystonie Vereniging. JD: Grants: Dutch organizations in scientific research, the Fonds Nutsohra, Jacques and Gloria Gossweiler foundation and Stichting Wetenschapsfonds Dystonie Vereniging. JV: advisory boards: Boston Scientific, Medtronic; grant support: Boston Scientific, Medtronic; Speaking fees: Boston Scientific, Medtronic, St. Jude, UCB, TEVA, and Allergan. MT: Grants: Netherlands organization for scientific research-NWO, Medium, Fonds NutsOhra, Prinses Beatrix Fonds, Gossweiler foundation, Stichting wetenschapsfonds dystonie vereniging, Phelps Stichting, educational grants and national DystonieNet grants from Ipsen and Allergan Famaceutics, Merz, Medtronic and Actelion.

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Clinical Practice: Evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin

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Cervical dystonia (CD) is the most frequent form of focal dystonia. Symptoms often result in pain and functional disability. Local injections of botulinum neurotoxin are currently the treatment of choice for CD. Although this treatment has proven effective and is widely applied worldwide, many issues still remain open in the clinical practice. We performed a systematic review of the literature on botulinum toxin treatment for CD based on a question-oriented approach, with the aim to provide practical recommendations for the treating clinicians. Key questions from the clinical practice were explored. Results suggest that while the beneficial effect of botulinum toxin treatment on different aspects of CD is well established, robust evidence is still missing concerning some practical aspects, such as dose equivalence between different formulations, optimal treatment intervals, treatment approaches, and the use of supportive techniques including electromyography or ultrasounds. Established strategies to prevent or manage common

Abbreviations: ADL, activities of daily living; BoNT, botulinum neurotoxin; CD, cervical dystonia; CMAP, compound muscle action potential; DBS, deep brain stimulation; EMG, electromyography; IU, international units; NAB, neutralizing antibodies; QoL, quality of life; RCTs, randomized controlled trials; SNR, secondary non-responsiveness; SPC, summary of product characteristics; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

side effects (including excessive muscle weakness, pain at injection site, dysphagia) and potential contraindications to this treatment (pregnancy and lactation, use of anticoagulants, neurological comorbidities) should also be further explored.

Keywords: botulinum toxin, cervical dystonia, recommendations, efficacy, side effects, treatment strategy

INTRODUCTION

Cervical dystonia (CD) is the most frequent form of focal dystonia, with an overall prevalence of 4.98/100,000 in Europe (1). CD is characterized by abnormal postures of head and neck that can considerably impair activities of daily living (ADL), with pain occurring in 43.1% of patients (2). Mood disorders, including anxiety and depression, are frequently present (3, 4).

Oral medication has a limited role. Trihexyphenidyl is classically proposed, but the tolerance profile is low (5). Benzodiazepines, especially diazepam and clonazepam, mainly reduce dystonia-related pain, anxiety, and possibly dystonic tremor (6). Tetrabenazine, although possibly effective (7), is limited by the frequent side effect of depression and parkinsonism. Evidence on the effectiveness of allied care treatments, including physiotherapy and cognitive behavioral therapy, is scanty (8). In those with unsatisfactory botulinum neurotoxin (BoNT) effect, surgery may be considered. Peripheral surgery, such as selective peripheral denervation, can provide improvement in about two-thirds of cases, with frequent relapses and is now rarely performed (9, 10). Deep brain stimulation (DBS) of the globus pallidus pars interna appears to be a better choice, despite potential severe complications (11). Alternative DBS targets, such as the subthalamic nucleus, need further investigation (12).

Local injections of BoNT are currently the treatment of choice for CD. By binding to peripheral cholinergic nerve endings in the neuromuscular junction, BoNT decreases the release of acetylcholine at the motor neuron in the synaptic cleft, thus blocking neuromuscular transmission and provoking muscle weakness (13).

Botulinum neurotoxin type A is the most frequently used; type B is only proposed in selected cases.

Although BoNT treatment is widely applied worldwide, many questions remain open in clinical practice.

Some aspects of this treatment have been largely explored in the literature, and robust evidence is available. Other aspects still deserve attention and univocal answers and directives are lacking.

In this paper, literature on BoNT treatment for CD was systematically reviewed based on a question-oriented practical approach. The aim was to provide practical recommendations on common issues in clinical practice.

To this end, we reviewed the evidence concerning the comparison of different formulations of BoNT in improving motor symptoms, pain, and quality of life (QoL), also in relation to the dosage conversion ratio, which is a long debated topic.

Another common issue in the daily practice, which demands stronger evidence is how to prevent and manage side effects and complications, including the formation of neutralizing antibodies (NAB) and treatment side effects such as dysphagia, neck muscle paresis, or pain at injection site.

Due to the nature of the treatment itself, which involves intramuscular injections and a neurochemical denervation, questions may arise concerning potential contraindications such as the use of anticoagulants or the presence of concomitant neuromuscular disorders, in addition to pregnancy and lactation.

We finally explored issues related to the optimization of the treatment, including the optimal initial dose of BoNT, and whether injection strategy can be improved by applying multiple injection points instead of single injection points or by using neurophysiological techniques or associated physiotherapy. These topics have been touched upon in some studies, but the use of different methodologies, protocols, and sometimes patients' populations makes it difficult to directly compare the results.

METHODS

The aim of this manuscript was to provide a literature review focused on some specific question arising from the clinical practice.

A structured literature review was conducted, by using appropriate keywords covering the topic of BoNT treatment for CD. A language restriction to English, French, German, and Dutch was applied. All kind of studies were reviewed and studies carried out before 1980 were excluded.

Information Sources

Three databases were searched: Medline and Embase using the Ovid interface, and the Cochrane library.

Selection of Papers

In all three databases, we identified systematic reviews, randomized controlled trials (RCTs), health economic evaluation studies, and, in both Medline and Embase, also observational studies. The complete search strategy is reported in File S1 in Supplementary Material.

Review Method

All the papers were screened for topic appropriateness on abstract basis by two independent reviewers with successive agreement on discrepancies. Papers were then assigned to different coauthors according to predefined key clinical questions.

To assess the quality of the published studies, the classification scheme for level of evidence and the level of recommendation of the American Academy of Neurology was used (14) (File S2 in Supplementary Material). The recommendation level is reported for each statement.

RESULTS

Effect of Different BoNT Formulations on CD (Table 1)

Three BoNT-A products are commercially available: onabotulinumtoxinA (Botox®, Allergan), abobotulinumtoxinA (Dysport®, Ipsen), and incobotulinumtoxinA (Xeomin®, Merz). These products differ concerning the added preservatives, the toxin solubility, and the relative potencies. Only one type of BoNT-B is available: rimabotulinumtoxinB (Neurobloc®/Myobloc®, Elan Pharma).

Are the Different Formulations of BoNT-A and BoNT-B Effective in Improving CD?

Several RCTs showed that onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB are effective in reducing dystonia when compared to placebo (15–25).

One RCT showed that incobotulinumtoxinA (at both doses of 120 IU and 240 IU) significantly improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total scores compared to placebo in 233 CD patients (26) and that improvement of mean TWSTRS-total ($p < 0.001$) and severity score ($p < 0.016$) persisted after repeated injection (up to 5) (27).

Conclusion and Recommendations

There is class I evidence that the three BoNT-A and the BoNT-B formulations significantly improve dystonia in CD. The recommendation level is A for abobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB, and level B for incobotulinumtoxinA (26).

TABLE 1 | Effect of different formulations of BoNT on CD.

Question	Answer	Level of recommendation
Is abobotulinumtoxinA effective in improving CD?	Yes	A
Is incobotulinumtoxinA effective in improving CD?	Yes	B
Is onabotulinumtoxinA effective in improving CD?	Yes	A
Is rimabotulinumtoxinA effective in improving CD?	Yes	A
Does BoNT-A treatment improve quality of life?	Yes	B
Does BoNT-A reduce pain associated with CD?	Yes	A
Do BoNT-A and BoNT-B have a comparable effect and duration of effect on dystonia?	Yes	A
Do BoNT-A and BoNT-B have the same rate of side effects?	No (side effects are more frequent with BoNT-B)	B
What is the conversion ratio of onabotulinumtoxinA to abobotulinumtoxinA?	1 IU to 3 IU 1 IU to 2.5 IU	A B
What is the conversion ratio of onabotulinumtoxinA to incobotulinumtoxinA?	1 IU to 1 IU	B

BoNT, botulinum neurotoxin; CD, cervical dystonia.

Does BoNT-A Treatment Improve QoL?

In a double-blind RCT, treatment with 500 IU of abobotulinumtoxinA produced significantly greater improvements than placebo in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains of the SF-36 ($p \leq 0.03$) (28).

Conclusion and Recommendations

There is class I evidence that BoNT-A improves QoL in CD (level B).

Does BoNT-A Reduce Pain Associated with CD?

In five RCTs with a total of 162 CD patients, 71% of the patients treated with onabotulinumtoxinA and abobotulinumtoxinA reported pain reduction compared with 12% of the patients in the placebo group ($p < 0.00001$) (29). Pain was also improved with incobotulinumtoxinA in both single-set injections and long-term treatment (26, 27).

Conclusion and Recommendations

There is class I evidence that BoNT-A reduces pain symptoms in CD (level A).

Do BoNT-A and BoNT-B Have Comparable Effects?

In two RCTs (30, 31), no difference was found in the size and duration of effect on the total TWSTRS score and sub-scores (dystonia severity, limitations, and pain score) between BoNT-A and BoNT-B. Dry mouth and swallowing difficulties were more common with BoNT-B (30, 32).

Conclusion and Recommendations

Botulinum neurotoxin-A and BoNT-B have a comparable effect and duration of effect (level A).

Side effects are more frequent with BoNT-B (class I evidence, level B).

What Is the Conversion Ratio of Different Formulations of BoNT-A?

The conversion factor between the different formulations is still a matter of discussion.

OnabotulinumtoxinA vs. AbobotulinumtoxinA

LD50 tests have shown 1:1 potency ratio of incobotulinumtoxinA vs. onabotulinumtoxinA (33), and 2.3:1 of abobotulinumtoxinA vs. onabotulinumtoxinA. These data however cannot be directly translated into the clinical practice (34).

In a retrospective study, changing from onabotulinumtoxinA to abobotulinumtoxinA with a conversion rate of 1:2 resulted in a tendency toward higher efficacy but more adverse events (35). At 6.5 years follow-up, the doses had been reduced, and the median dose conversion ratio had decreased to 1:1.7.

In a double-blind study, 79 healthy controls were randomized into 18 groups, receiving different doses and concentrations of onabotulinumtoxinA or abobotulinumtoxinA (36). Both toxins caused a comparable, significant decline in the compound muscle action potential (CMAP). A statistical model with

CMAP data indicated a bioequivalence of 1 IU onabotulinumtoxinA:1.57 IU abobotulinumtoxinA and a maximum dose-equivalence ratio of 1:3.

In a comparative clinical study, 73 CD patients were randomized for onabotulinumtoxinA or abobotulinumtoxinA with a dose ratio of 1:3 IU (37). The improvement of Tsui score, the duration of effect, and the rate of side effects were comparable.

Two different conversion factors (1:3 and 1:4) between onabotulinumtoxinA and abobotulinumtoxinA were tested in a double-blind randomized three-period crossover study in 54 CD patients (38). AbobotulinumtoxinA was significantly more effective than onabotulinumtoxinA in reducing Tsui score, with no significant difference between the two conversion ratios. The adverse events were more frequent in the abobotulinumtoxinA group, but only significantly for the 1:4 conversion.

A recent double-blind, randomized, crossover study using a conversion ratio of 1:2.5 IU showed comparable efficacy and adverse effects (39).

Conclusion and Recommendations

It is recommended to use a conversion of 1 IU onabotulinumtoxinA to 3 IU abobotulinumtoxinA (level A) (37, 38), although conversion ratios of 1:2.5 might be equally safe and effective (class I, level B) (39).

OnabotulinumtoxinA vs. IncobotulinumtoxinA

In an open label prospective crossover study, 40 patients initially treated with onabotulinumtoxinA were randomly assigned to treatment switch to incobotulinumtoxinA with a 1:1 ratio (33). Inter-injection intervals and treatment duration showed comparable efficacy for at least four injection cycles. Comparable efficacy on TWSTRS and adverse-event profiles for up to 16 weeks were also reported in a randomized, double-blind, parallel-group, non-inferiority trial, with CD patients randomized to incobotulinumtoxinA or onabotulinumtoxinA with the same conversion factor of 1:1 (40).

Conclusion and Recommendations

It is recommended to use a conversion of 1:1 IU onabotulinumtoxinA to incobotulinumtoxinA (class I, level B).

Optimization of BoNT Treatment for CD (Table 2)

What Is the Recommended Initial BoNT Dose for Treatment of CD?

According to the respective summary of product characteristics (SPC—last accessed 08/04/2015), the suggested starting total dose is 500 IU in two-three muscles, for abobotulinumtoxinA (SPC last text revision 11/12/2013), and <200 IU (50 IU/injection and maximum 100 IU to the sternocleidomastoid) for onabotulinumtoxinA (SPC, 19/03/2015). For incobotulinumtoxinA, a total dose of 200 IU is mentioned, with doses up to 300 IU allowed (50 IU/injection—SPC, 16/11/2012). For rimabotulinumtoxinB, an initial dose of 5,000 IU may be considered, but a dose of 10,000 IU divided between two and four muscles may be more effective (SPC, 26/02/2014).

TABLE 2 | Optimization of BoNT treatment for CD.

What is the recommended initial dose for treatment of CD with abobotulinumtoxinA?	500 IU (although other dosages might be used)	A
What is the recommended initial dose for treatment of CD with incobotulinumtoxinA?	120 IU	B
What is the recommended initial dose for treatment of CD with onabotulinumtoxinA?	No recommendation	U
What is the recommended initial dose for treatment of CD with rimabotulinumtoxinB?	2,500 or 5,000 IU 10,000 IU	B A
Can prior polymyographic EMG (pEMG) and EMG guidance improve the treatment outcome in treatment-naïve patients?	Yes	A
Can prior pEMG and EMG guidance improve the treatment outcome in patients with deterioration of treatment effect?	Yes	C
Are multiple-points injections per muscle more effective than single-point injections?	Yes	U
Can additional physiotherapy improve the effect of BoNT treatment?	No (motor improvement as measured by TWSTRS or Tsui score) Yes (disability and pain and prolongs the effect of BoNT)	C U

BoNT, botulinum neurotoxin; CD, cervical dystonia; EMG, electromyography; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

In an RCT, 73 patients were randomized into four groups treated with placebo, abobotulinumtoxinA 250, 500, or 1,000 IU, divided between one splenius capitis and the contralateral sternocleidomastoid muscle (21). The greatest improvement was found in the group treated with 1,000 IU, although significantly more side effects were reported. An initial dose of 500 IU abobotulinumtoxinA (divided into 100–200 IU in the sternocleidomastoid muscle, 250–350 IU in the splenius, 100–200 IU in the trapezius, and 100–200 IU in the levator scapulae) significantly improved CD with respect to placebo in another RCT on 68 patients (41). Based on these results, an initial dose of 500 IU abobotulinumtoxinA is suggested. It is worth mentioning, however, that CD could be successfully treated using an average total dose of 200–400 IU abobotulinumtoxinA under electromyography (EMG) guidance, resulting also in fewer side effects (42).

A starting dose of 50–100 IU of onabotulinumtoxinA per muscle, with a maximum dose per session of 280 IU, was used in a study on 32 patients. A documented improvement in both subjective and objective parameters was observed in 75% of patients (43). The mean total doses of original onabotulinumtoxinA injections, reported in 30 studies, as assessed by a systematic review, ranged from 60 to 374 IU in total (44).

In an RCT, both doses of 120 IU and 240 IU incobotulinumtoxinA significantly improved the TWSTRS-total scores compared to placebo in previously treated and treatment-naive subjects, with mild side effects. Initial dose 120 IU of incobotulinumtoxinA has been suggested based on these results (26).

Three double-blind, randomized, placebo-controlled studies (20, 22, 23) have shown that the effect of botulinum toxin B

injections in doses of 2,500, 5,000, and 10,000 IU was significantly higher compared to placebo, with the highest clinical effect seen with dose of 10,000 IU as measured by the TWSTRS-total score. The incidence of mild dysphagia was higher in the 10,000 IU group (16, 10, and 27%, respectively, as compared to no patient who received placebo) (20).

Conclusion and Recommendations

An initial total dose of 500 IU abobotulinumtoxinA is effective (level A), although other dosages might be used (41, 45).

An initial total dose of 120 IU incobotulinumtoxinA is probably effective (evidence class I, level B) (26).

No clear recommendations can be given on the optimal starting does of onabotulinumtoxinA (level U).

An initial total dose of 2,500 or 5,000 IU rimabotulinumtoxinB (evidence class I, level B) or 10,000 IU (level A) is probably effective.

Can Prior Polymyographic EMG (pEMG) and Simultaneous EMG Improve the Treatment Outcome?

In one RCT, 52 CD patients were randomized into a pEMG-group (treated muscles selected based on clinical evaluation and pEMG, and BoNT injected using simultaneous EMG) or control group (muscles selected based solely on clinical examination and injected without EMG) (46). Improvement on the TWSTRS was higher in the pEMG with EMG assistance group (14 vs. 5%).

In a randomized prospective, blinded study on 26 treatment-naive patients, the objectively measured clinical outcome was significantly better when the muscle selection was based on quantitative EMG and treatment was performed with simultaneous EMG, than when treatment was based on clinical judgment alone (47).

Other studies showed that without pEMG, 24–41% of the dystonic muscles were missed, and 25–35% of the injected muscles were misjudged as dystonic (47–49).

A retrospective study explored results of treatment with pEMG in 40 patients with previously unsatisfactory treatment response (50). After 1 year, a significant improvement in both Tsui scores and subjective evaluation was observed. pEMG led to change in injection pattern in 96% of the patients.

In another study, 8/10 CD patients with deterioration of treatment effect, achieved marked improvement (64% on TWSTRS) after pEMG guided injections (51).

The identification of motor endplate zones with high-density surface EMG may help decreasing the BoNT dose by keeping the effect unaltered (52).

Conclusion and Recommendations

There is class I evidence that, in treatment-naïve patients, improvements in dystonia and pain are greater if muscles are selected based on a combination of clinical examination and pEMG and injections are performed with EMG guidance (level A) (46, 47).

In patients with deterioration of treatment effect, the use of pEMG and EMG guidance can improve the results (class III, level C) (50, 51).

Are Multiple-Points Injections per Muscle More Effective than Single-Point Injections?

No RCTs on this topic were found. A comparative study in 49 patients showed that multiple injections are more effective than a single injection in improving dystonia, pain, posture deformity, range of motion, and activity endurance (53). Experts recommend the administration of one to four injections per muscle, depending on the volume of the muscle (4, 54).

Conclusion and Recommendations

There are indications (class III) that multi-point BoNT injections are more effective than single-point BoNT injections (level U).

Can Physiotherapy Improve the Effect of BoNT Treatment?

In one single-blind RCT, no significant difference was found between patients randomized to BoNT treatment combined with relaxation therapy alone or with a 12-week physiotherapy program and relaxation therapy (55).

In one crossover RCT on 40 patients, significantly greater reductions in disability in ADL and subjective pain were observed after a 6-week additional physiotherapy, with respect to BoNT treatment alone. In addition, clinical benefit lasted longer and a lower BoNT dose was needed at reinjection. No significant differences were observed on the Tsui scale and TWSTRS (56).

In a case–control open study, 40 patients followed a 4-week physiotherapy program combined with BoNT treatment or BoNT treatment alone. The physiotherapy group showed significantly more improvement on the pain subscale of the TWSTRS, and on some subscales of the SF-36 (57).

Conclusion and Recommendation

Adding physiotherapy in combination with BoNT treatment does not produce a greater motor improvement as measured by TWSTRS or Tsui (class II, level C) (55).

Adding physiotherapy to BoNT treatment may improve disability, pain, and prolong the effect of BoNT [class III (4) and IV (57), level U].

Primary and Secondary Non-Responsiveness (SNR) (Table 3)

Primary non-responsiveness to BoNT, defined as lack of treatment effect from the first application, and due to genetically induced resistance (58) or a prior (unnoticed) botulism (59), is exceptional. Technical aspects such as insufficient dosing, errors during drug storage and reconstitution, or improper injection sites could also lead to an initial lack of response, usually amended in successive treatments.

Secondary non-responsiveness is defined as "insufficiently improved posture after three or more unsuccessful injection cycles in CD patient's previously achieving satisfactory results" (60). SNR concerns around 3–5% of the patients (61).

The formation of NAB, with estimated frequency in CD patients varying from 1.2% (62) to 40% (63), is one of the causes of SNR. NAB have been found in patients treated with

TABLE 3 | Primary and SNR.

Are treatment intervals <12 weeks safe?	Yes (incobotulinumtoxinA)	U
	No recommendation (rimabotulinumtoxinB, onabotulinumtoxinA, and abobotulinumtoxinA)	U
Which treatment strategies are useful in case of non-response to BoNT-A treatment?	Keeping the treatment intervals constant (early detection of SNR)	U
	Repeated plasma exchange (contrasting NAB-induced SNR)	U
	Switching to BoNT-B produces only temporary benefit	U

BoNT, botulinum neurotoxin; NAB, neutralizing antibodies; SNR, secondary non-responsiveness.

onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB (64). RimabotulinumtoxinB seems more likely to elicit SNR than BoNT-A: antibody-induced therapy failure was shown in 44% of CD patients treated with BoNT-B during a short period (65). The development and titer of NAB does not correlate with the entity of SNR, and there is evidence that the mere detection of NAB does not necessarily indicate the presence of SNR (66, 67). No antibodies are described after treatment with incobotulinumtoxinA in naive CD patients (68, 69), while this has been reported in one patient previously treated with another BoNT (33).

Factors significantly associated with SNR include previous recourse to other therapies such as surgical interventions, physical therapy and neuroleptic use, a higher number of serious adverse events, more frequent treatment interruptions, and higher average BoNT-A doses during the last three injection cycles (67).

Are Treatment Intervals <12 Weeks Safe?

No controlled studies have compared the long-term immunogenicity of different BoNT-A.

In a consensus statement, experts recommend that reinjection is left as long as clinically possible, to minimize the chance of antibody responses (4).

The current manufacturer information suggest that the minimal interval between injections should be 10 (SPC onabotulinumtoxinA and incobotulinumtoxinA) to 12 weeks (SPC abobotulinumtoxinA). This information, however, was based on data obtained with the original formulation of onabotulinumtoxinA, which contained a higher protein load (70, 71).

Fixed 3-month intervals may result in a decrease in treatment satisfaction toward the end of the period. Indeed up to 45% of patients indicated a preference for treatment intervals ≤10 weeks (72).

In a trial with incobotulinumtoxinA, where injection sessions were administered at intervals of 6–20 weeks, there were no differences in the tolerability profile in the group of patients injected at 6–14 weeks with respect to the other groups (27).

Conclusion and Recommendations

There is only one class I study showing that, with incobotulinumtoxinA, treatment intervals <12 weeks do not increase the risk of developing antibodies. There is insufficient data to recommend or discourage the use of an interval <12 weeks for treatment with rimabotulinumtoxinB, onabotulinumtoxinA, and abobotulinumtoxinA (level U).

Which Treatment Strategies Are Useful in Case of SNR to BoNT-A Treatment?

Secondary non-responsiveness develops gradually, starting with a reduced duration of clinical effect and culminating with significant reduction of the maximal effect (73). Therefore, constant treatment intervals and careful scoring of treatment effect may lead to an early detection of SNR (74). However, whether an early detection is useful to prevent the development of SNR and the induction of high titers of NAB is unclear, considering the absence of effective prevention strategies.

Switching from BoNT-A to BoNT-B in patients with SNR due to NAB may initially result in effective treatment; however, most of these patients will eventually develop antibodies to BoNT-B as well (75, 76).

Neutralizing antibodies depletion by repeated plasma exchange in one patient with SNR, allowed recovery of BoNT-A treatment effect (77).

Conclusion and Recommendations

It is suggested that keeping the treatment intervals constant may lead to early detection of SNR (level U).

Repeated plasma exchange is possibly effective in contrasting NAB-induced SNR (level U).

Switching to treatment with BoNT-B produces only temporary recovery of effect, often followed by development of antibodies against BoNT-B (level U).

Management of Side Effects of BoNT Treatment (Table 4)

What Is the Most Effective Strategy to Avoid Dysphagia following BoNT Treatment?

Swallowing difficulty is caused by BoNT spreading to the throat muscles. Bilateral sternocleidomastoid injections are more frequently associated with dysphagia (54). Dysphagia is often mild (severe in <5% of the cases), very rarely requires hospitalization or feeding tube, and disappears gradually after 2–3 weeks (54). Dysphagia is relatively common: 7.1% of the patients reported dysphagia after treatment with the original onabotulinumtoxinA, 3.4% with the new generation onabotulinumtoxinA, 19.4% with abobotulinumtoxinA, 12.6% with incobotulinumtoxinA, and 15.6% with rimabotulinumtoxinB (26, 44, 78). Different tendency to spread into surrounding muscles could rely on differences in formulation, size of the protein molecules, or dilution factor, although these results are based on heterogeneous studies in terms of patient selection, dose, and injected muscles (44).

In a study, five CD patients who had reported 34 episodes of dysphagia over 98 EMG-guided injections (34.7%) were treated with additional use of ultrasounds: this resulted in no episodes of dysphagia across 27 injection sessions (79).

Conclusion and Recommendations

The additional use of ultrasound may lessen recurrent dysphagia after botulinum treatment (class IV, level U).

TABLE 4 | Side effects and contraindications of BoNT treatment for CD.

What is the most effective to avoid dysphagia?	The additional use of ultrasound may lessen recurrent dysphagia	U
What is the most effective strategy in case of neck muscles paresis?	The use of a soft collar can relieve the symptoms of neck extensor muscles paresis	U
What is the most effective strategy to prevent injection pain?	Skin cooling or local application of anesthetic cream reduce injection pain	U
Is BoNT treatment safe during pregnancy and lactation?	BoNT treatment during pregnancy and lactation is not recommended and should be avoided whenever possible	U
Is BoNT treatment safe for CD patients who use anticoagulants?	The risk of hematoma following BoNT treatment by concomitant use of coumarin derivatives is low	U
Is BoNT treatment safe for CD patients with concomitant neurological comorbidities?	Patients with concomitant impairment of neuromuscular transmission may experience clinical deterioration after BoNT treatment, although in selected cases treatment might be safe and beneficial	U

BoNT, botulinum neurotoxin; CD, cervical dystonia.

What Is the Most Effective Strategy in Case of Neck Muscles Paresis following BoNT Treatment?

Weakness of the neck extensors is a common side effect of BoNT treatment in these muscles. The symptoms are usually mild and are generally resolved within a few weeks (54). According to a systematic review, this side effect was reported by 62/339 (18%) of the patients treated with onabotulinumtoxinA or abobotulinumtoxinA, compared with 9/266 (3%) of the patients in the placebo group (80). In an RCT on 233 patients, neck weakness was reported in 6–10% of patients treated with incobotulinumtoxinA 120 or 240 IU, respectively, as compared to 1% of patients treated with placebo (26).

There is no evidence to support the use of a soft collar, although this measure can relieve symptoms of paresis (4).

Conclusion and Recommendations

The use of a soft collar can relieve the symptoms of neck extensor muscles paresis (class IV, level U).

What Is the Most Effective Strategy to Prevent Pain at the Injection Site?

In RCTs comparing BoNT-A treatment to placebo, injection pain occurs equally in both groups (4). This pain is usually present for only a few days and is rarely a reason to terminate the BoNT-A treatment (54).

Skin cooling (with ethylchloride spray, dry cold, or ice) or local application of anesthetic cream decreases pain associated with limb or facial botulinum injections (81–83). As such, they may be beneficial in patients for the treatment of CD too, although no specific studies were found.

Conclusion and Recommendations

Skin cooling or local application of anesthetic cream can reduce injection pain (class IV, level U).

Contraindications for BoNT Treatment (Table 4)

Is BoNT Treatment Safe during Pregnancy and Lactation?

OnabotulinumtoxinA is classified as pregnancy Category C by FDA: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. This drug should be used during pregnancy only if the benefit outweighs the risk to the fetus." Animal studies have provided no indications of harm during pregnancy with doses of BoNT-A normally used in clinical practice (84).

Results of a survey on 396 doctors showed that a total of 16 pregnant women had been treated with BoNT, primarily in the first trimester. One patient (8.3%) had a miscarriage, while the other patients gave birth to healthy children after full-term pregnancies (85).The overall risk of miscarriage, regardless of the cause, is 15–20% (86). In the literature, up to 25 women are described who have been treated during each stage of pregnancy: two miscarriages were reported in women with previous history of miscarriage; the other cases reported uneventful pregnancy and healthy children (87).

No studies were found on the use of BoNT during lactation. Due to insufficient data, the manufacturers do not recommend using BoNT during lactation, although it seems unlikely that BoNT may enter breast milk (84).

Conclusion and Recommendations

Although several cases have been reported of safe use of BoNT during pregnancy, the effect of BoNT on the unborn child has been insufficiently studied in humans; therefore, BoNT treatment during pregnancy is not recommended and should be avoided whenever possible (class IV, level U).

No studies have been conducted on the effect of BoNT on the nursing child; to exclude side effects, BoNT treatment should be avoided during lactation (class IV, level U).

Is BoNT Treatment Safe for CD Patients Who Use Anticoagulants?

No reports of complications resulting from the use of coumarin derivatives or non-vitamin K antagonist oral anticoagulants by CD patients treated with BoNT were found. According to the SPC of coumarin derivates, intramuscular injections are discouraged (but not explicitly forbidden) because of the increased risk of hematomas, while no limitation is reported for subcutaneous injections. The incidence of hematoma after BoNT injection was marginally increased in a group of 32 patients treated with phenprocoumon (3%) with respect to 32 control patients (1.8%) (88).

Conclusion and Recommendations

The risk of hematoma following BoNT treatment by concomitant use of coumarin derivatives has not been sufficiently studied but seems low (class IV, level U).

Is BoNT Treatment Safe for CD Patients with Concomitant Neurological Comorbidities?

Treatment with BoNT may exacerbate symptoms of coexistent neuromuscular diseases (89, 90) or unmask subclinical cases (91, 92). Myasthenia gravis, amyotrophic lateral sclerosis,

and Lambert–Eaton diseases are reported as contraindications to BoNTs treatment in the respective SPCs, although cases of safe CD treatment in patients with myasthenia or amyotrophic lateral sclerosis have occasionally been reported (93, 94).

Generalized weakness has been rarely reported after BoNT injections, most frequently in patients treated for spasticity (95, 96).

Conclusion and Recommendations

Patients with preexistent impairment of neuromuscular transmission may experience clinical deterioration after BoNT treatment, although in selected cases treatment might be safe and beneficial (class IV, level U).

GENERAL CONSIDERATIONS

Overall, there is a solid bulk of evidence supporting a good beneficial effect of the different formulations of BoNT in the treatment of CD, with a good benefit-to-risk ratio and a sustained effect over time. However, there is still room for strategies to further improve the efficacy and safety of this treatment. Robust evidence is missing concerning some practical aspects, such as treatment approaches, and the use of supportive techniques including EMG or ultrasounds. Existing knowledge often comes from secondary outcome measures in larger studies designed for other research questions. These studies often use variable methods and outcome measures, which makes comparisons difficult. Future studies should focus on these topics, by using standardized approaches and focusing on only one research question.

It has been noticed that the reported results are not always applicable to the daily practice. This may partly be due to the fact that, in the case of BoNT, optimal treatment requires some variability, according to the needs of the patients and to the progression of the symptoms. The design of future studies should also take this aspect into account.

Although the incidence of adverse events related to BoNT injections, including the formation of NAB, is low, there is a need for established strategies to prevent or manage common side effects of this treatment. To this end, multicentre collaborations are warranted in order to be able to collect an informative number of cases.

Some of the main clinical questions, including the dose equivalence between different formulations and the minimum safe treatment intervals, are matter of discussion already for several years. This knowledge gap could only be addressed by research groups willing to engage in well designed and adequately powered clinical studies.

The continuous commitment of clinicians and basic scientist to produce robust evidence concerning these and other open questions arising from the clinical practice, is fundamental to improve QoL of CD patients.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception of the work, drafted sessions of the manuscript or revised it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00035/full#supplementary-material.

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Recognizing the Common Origins of Dystonia and the Development of Human Movement: A Manifesto of Unmet Needs in Isolated Childhood Dystonias

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Dystonia in childhood may be severely disabling and often unremitting and unrecognized. Considered a rare disorder, dystonic symptoms in childhood are pervasive in many conditions including disorders of developmental delay, cerebral palsy (CP), autism, neurometabolic, neuroinflammatory, and neurogenetic disorders. Collectively, there is a need to recognize the role of early postures and movements which characterize phases of normal fetal, infant, and child development as a backdrop to the many facets of dystonia in early childhood neurological disorders and to be aware of the developmental context of dystonic symptoms. The role of cocontraction is explored throughout infancy, childhood, young adulthood, and in the elderly. Under-recognition of pervasive dystonic disorders of childhood, including within CP is reviewed. Original descriptions of CP by Gowers are reviewed and contemporary physiological demonstrations are used to illustrate support for an interpretation of the tonic labyrinthine response as a manifestation of dystonia. Early recognition and molecular diagnosis of childhood dystonia where possible are desirable for appropriate clinical stratification and future precision medicine and functional neurosurgery where appropriate. A developmental neurobiological perspective could also be useful in exploring new clinical strategies for adult-onset dystonia disorders focusing on environmental and molecular interactions and systems behaviors.

Keywords: dystonia, developmental dystonia, cocontraction, tonic labyrinthine response, cerebral palsy, Gowers, genetic heterogeneity, phenotypic pleiotropy

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We present a "Manifesto of Unmet Needs in Childhood Isolated Dystonias" (summarized in Panel 1. A Manifesto of Unmet Needs in Isolated Childhood Dystonias in Appendix), partly to encourage recognition of dystonia as an important cause of morbidity in children, to stimulate work capturing how dystonia affects the lives of children by using appropriate outcome measures and to develop new strategies for managing dystonias in a timely fashion.

Dystonia (see Panel 2. Dystonia, Dyskinesia, and Hypertonus in Appendix for current and historical definitions) in childhood may be severely disabling and often unremitting (1). Considered a rare disorder, dystonic symptoms in childhood are pervasive in many conditions including disorders of developmental delay, CP, autism, neurometabolic, neuroinflammatory, and neurogenetic disorders. Collectively, there is a need to recognize the role of early postures and movements, which

characterize phases of normal fetal, infant, and child development as a backdrop to the many facets of dystonia in early childhood neurological disorders and to be aware of the developmental context of dystonic symptoms.

The predicament of a child facing a life with dystonia today has improved considerably over the past 20 years. New genetic diagnoses and complex neurosurgical solutions such as deep brain stimulation, highlight as never before, the need for even greater clinical-diagnostic skill to adequately characterize the clinical phenomenology and select the optimal management within an appropriate time-frame. Children with dystonia need a "manifesto" to guide clinical research programs and focus the resources of the clinical and scientific communities.

THERE IS A NEED TO RECOGNIZE THE IMPORTANCE OF EARLY EXPERIENCE OF MOVEMENT FOR THE FETUS AND INFANT AND ENVIRONMENTAL EFFECTS ON THIS EARLY DEVELOPMENT

The phenomenon of dystonia can best be understood in the context of the phylogeny (evolution) and ontogeny (development) of the motor system. This approach indicates that dystonic postures and movements leading to twisting and writhing patterns of movement (see Panel 2. Dystonia, Dyskinesia, and Hypertonus in Appendix) are innate features of early human life. A fundamental question may be posed: could the fetus, newborn, or infant develop a motor repertoire if the early default state was one of akinesia?

Nature has already provided ample evidence that the answer is emphatically negative. The akinetic fetus is invariably born with severe contractures, often without appropriately developed joint cavities in what is termed the fetal-akinesia deformation sequence with dire consequences for future survival and motor development (2). Externally acquired mechanisms of paralysis with neuromuscular paralyzing agents (3, 4), effects of maternal tetanus on fetal movements (5), or antibodies to the human fetal neuromuscular junction acetylcholine receptors, produce early akinesia with similar effects (6–8) and genetic defects in neuromuscular junction acetylcholine receptor proteins likewise (9). Immobility may not only impair or abolish joint cavity formation in flaccid paralysis (10) but also profoundly affect bone growth (10), an effect also seen after rigid immobility (11) following brain injuries to the chick embryo. Movement or motion itself is therefore essential for the development of a functional musculoskeletal system in the fetus and infant. In this respect, it is remarkable that the human fetus engages 11 separate patterns of movement of increasing complexity as gestation progresses including "twitches," "independent limb," "isolated head" movements or "combination movements," "quazi-startle" (sudden), or "hand-face" movements as well as "isolated body extension" and "thumb sucking," long before the onset of breathing movements at 18 weeks gestation (12). These early patterns of movements often following a dermatome–myotome relationship could be seen as fetal precursors of the "geste antagoniste" postures seen in later life, which are so successful in abolishing dystonia.

After delivery, the mammalian motor system is not yet anatomically committed to the adult arrangements. Remarkably, polysynaptic innervation of agonist–antagonist muscle pairs across a limb-joint is altered by the experience of motion (13–17). There then follows postnatal redundant axon elimination in health (14, 15, 17, 18) that occurs abruptly (19). But polysynaptic innervation may persist following external interventions to the muscle–tendon complex, for instance tenotomy in newborn rats, which results in a lack of activity-dependent normal synapse elimination (20). Similar results arise after chronic use of local anesthetics to block nerve conduction, which is associated with persistence of newborn polysynaptic innervation patterns (21, 22). These events may be relevant to ex-preterm or sick neonates who move less while undergoing neuromuscular paralysis for mechanical ventilator support as described above. But it is not known how typical synaptic pruning is influenced by excessive movement.

Increased "reciprocal excitation" in healthy young infants is lost in adults indicating a physiological maturation of the reciprocal stretch reflexes in normal development but this reciprocal excitation is retained in children with cerebral palsy (CP) due to perinatal injuries (23, 24), thus favoring persistence beyond early infancy of cocontraction muscle synergies.

A NEED TO RECOGNIZE THE LINK BETWEEN CHILDHOOD DYSTONIAS AND PATTERNS OF MOVEMENT AND POSTURES IN THE INFANT AND TODDLER. THIS INVOLVES RECOGNIZING THE KEY PATTERNS OF EMERGENT MOTOR DEVELOPMENT AND APPLYING OPERATIONAL DEFINITIONS THAT ENABLE RECOGNITION OF THESE KEY PATTERNS, INCLUDING UNDERSTANDING THE LINK BETWEEN DEVELOPMENTAL DYSTONIA AND PATHOLOGICAL DYSTONIA AT ALL AGES OF LIFE

In addition to the remodeling of the innervation of agonist–antagonist muscle pairs of the peripheral neuromuscular system, the fetus and infant undergo centrally driven truncal, arm and leg flexor, and extensor postural stages (25).

The cerebral glucose metabolism of the preterm and full-term baby shows that the dominantly flexed postures with apparently "dystonic-athetoid" movements are associated with mainly thalamic and brain stem and cerebellar glucose metabolic activity (26). It can be hypothesized that in developmental terms, persistent flexed trunk and limb postures are dominated by thalamic activity and the term newborn represents "*Dystonic–Athetoid Thalamic Man*."

By 3–4 months of age, the infant trunk adopts a symmetrically straight posture, there is head control and the back is straight in supported sitting or standing, but the arms and legs are hyperactive in what can only be described as dancing movements, i.e.,

"physiological or developmental chorea," representing "*choreiform man*": parents may even refer to their infant performing the popular Irish dance: "*Riverdance*."

By 6–8 months, seemingly purposeless chorea is replaced by directed and targeted swatting and kicking movements of arms and legs. This represents the "*Kung-Fu Man*" phase when arms and legs appear to share common skills in accessing targets which occurs before the legs acquire a locomotor role. This pre-locomotor "equipotential" phase of motor abilities in all four limbs underpins the capacity of feet to be used as hands in naturally occurring limb-deficit impairments such as "*phocomelia*" when the arms may be entirely missing and the feet are used for manual tasks. Another description of this phase of motor development could be the "*democratic phase of all four limbs*," which is only witnessed in the pre-weight-bearing and pre-locomotor phase of human development.

This period of development also coexists with intermittent dystonic posturing including simultaneous leg extension-hip-abduction or adduction postures, equinovarus foot posturing, spontaneous extensor great toes, and fanning of the toes, which are often referred to as "*striatal toes*."

At 6–10 months, the infant develops the ability to play with the feet and adopt "*ballerina*" poses, often holding the legs straight up in the air and playing with the feet. These postures dissipate soon after the legs are committed to locomotor tasks, either when bottom-shuffling or the development of bi-pedal ambulatory mobility (Lin, unpublished results).

Ballerina posturing of the legs can also be seen in young children with isolated monogenic dystonia due to the Torsin-A mutation (*DYT*-1). These developmental motor patterns are illustrated in **Figure 1**, including the fetal leg extension postures and typical infant leg "stereotypies" at 6 months of age and the ballerina posturing in DYT-1 dystonia as an illustration of the link between dystonic postures and movements and early physiological postures and movements.

AN UNMET NEED TO RECOGNIZE THE SIMILARITIES AND DIFFERENCES BETWEEN DEVELOPMENTAL COCONTRACTION, TASK-DEPENDENT COCONTRACTION, THE PATHOLOGICAL COCONTRACTION OF DYSTONIA, OBSERVATIONS OF SELECTIVE MOTOR CONTROL, AND SURROUND INHIBITION IN CHILDREN, THE ELDERLY, AND IN DYSTONIC INDIVIDUALS

As briefly reviewed, the embryo, fetus, and young infant must be hyperkinetic to overcome gravity and the risk of early intrauterine and extra uterine deformity, respectively. Another function of hyperkinesia is refinement of the initially clumsy, goal-directed motor behaviors, by harnessing activity-dependent plasticity for the successful transition from "goal-directed movements" (which require conscious direction) to "habitual movements" (27). Habitual movements are internalized, semi-automatic movements that can be executed as part of more complex tasks such as reaching, holding, and using tools, or, for the legs, for ambulatory and propulsive tasks.

In older children and adults, weight-bearing limbs have high inertia and low muscle stiffness whereas limbs for fine, non-repetitive, and complex movements such as our digits have low inertia and high muscle stiffness. This arrangement ensures that our limbs can resist unwanted oscillation using inertia for the legs and intrinsic hand muscle stiffness for the fingers and toes, wrists, and ankles without expending unnecessary energy through muscle activation (28).

How Does the Motor System Adapt from Infancy to Adulthood?

A reasonable explanatory narrative for these dramatic alterations in motor properties is that in early infancy the muscles and tendons have very high compliance, i.e., reduced stiffness (28), the mechanical–anatomical consequences of which are compensated for by active cocontraction in all tasks, leading to a stiff-jerky, coarse movement repertoire, rather than the skilled-economical motor repertoire of later years. Muscles are also different in infancy and early childhood, reflex muscle twitches being weak and slow to contract and relax (28, 29), contributing to coarse movement patterns on attempting skilled tasks (30). Developmental cocontraction (31), i.e., *developmental dystonia*, compensates for reduced intrinsic stiffness and low limb-inertia in early life (28–30).

Panel 3. Causes of Cocontraction in Children in Appendix summarizes the phases of developmental physiological cocontraction, task-dependent cocontraction, pathological cocontraction, and the return of cocontraction in the infant and the elderly (**Figures 4A–D**).

Early Movements and Postures and Cocontraction

Developmental Cocontraction and Joint-Synergies in Early Standing and Walking

When an infant first stands, the posture is typically stooped forward, arms abducted, fingers spread, legs widely abducted (spread apart), hips, knees, and ankles flexed, i.e., the "triple flexion" joint-synchrony posture. This triple-flexion muscle activation pattern produces the characteristic "crouch posture" and "crouch gait" of early infancy. However, this crouch posture is also the hallmark of the standing pattern in CP and of course in other later-acquired motor disorders. Because the crouch posture is so tiring (the reader can prove this to themselves by adopting a crouch stance while reading this text), infants and children and young adults may automatically replace ankle dorsiflexion with an *equinus posture*, i.e., by going up on tip-toes, which relieves some of the strain on the knee extensors. Thus, ankle equinus, which mechanically promotes biomechanical knee extension, is less tiring than an ankle crouch (dorsiflexion) posture. But standing in equinus is less mechanically stable than standing plantargrade. Both crouch and equinus gait and stance are associated with muscle cocontraction.

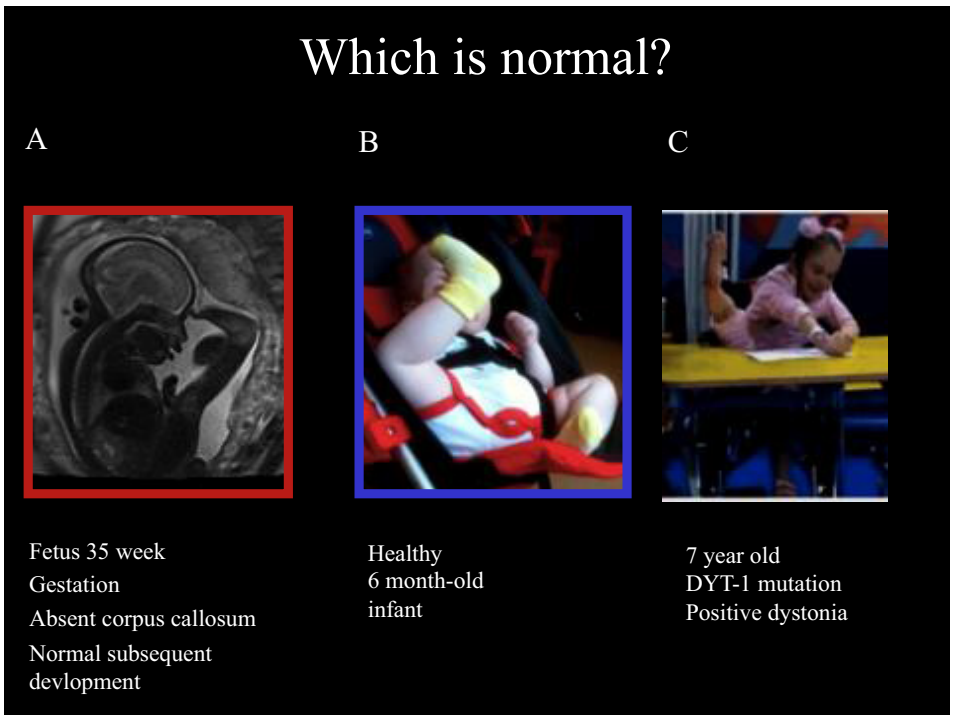

FIGURE 1 | **Fetal, infantile and pathological ballerina posturing dystonia**. Ballerina posture in 35-week gestation fetus with absent corpus callosum and subsequently normal development **(A)**, healthy 6-month old infant **(B)**, and a 7-year old girl with typical-onset isolated monogenic dystonia secondary to the DYT-1 mutation for the past 11 months **(C)**. The dystonia began in the left leg, spread to the right leg enforcing wheel-chair mobility after 6 months then spread to the arms: note shoulders hunched, arms extended to write, and left leg extension under the table with "ballerina" right leg posturing associated with equinovarus posturing at the right ankle. These pictures illustrate that "ballerina posturing" is common in infancy but pathological after the first year of life. The dystonia posturing may be considered a release of formerly dominant movements and postures of the legs before independent floor locomotion, standing, and walking. It is noteworthy that the ballerina posturing of the right leg was abolished as soon as the 7-year old girl regained independent standing 1 month after DBS. This reinforces the link between dystonic postures and functional levels. In this case, a transient regression to infantile posturing is brought about by dystonia.

It is well known that infants exhibit stiff and jerky movements when standing and walking with support, which, together with the joint-synchrony posture and movement pattern is underpinned by cocontraction of most trunk and limb muscle groups required for these tasks; gradually developing more fluent and economical movements when supported walking is replaced by unsupported walking, and cocontraction is replaced with a graceful interplay of agonist–antagonist muscles (31).

Heel-Strike as a Hallmark of the Mature Gait

The first hallmark of a mature gait pattern is the '*heel-strike*' at initial foot contact. But this seldom occurs before approximately 2 years of life, and then not for all 2-year olds.

The second hallmark of the mature gait is the advent of asynchronous joint patterns during the swing-phase of gait, i.e., *hip flexion-knee-extension-ankle dorsiflexion*, this last also producing the famous heel-strike of a mature gait.

The third hallmark of a mature gait is the contralateral arm swing. In this, the humerus swings forward synchronously with the contralateral femur of the "*swing*" leg. This pattern is similar to the crossed innervation pattern of the quadruped or vertebrate locomotor pattern. This is present when the infant crawls and is suppressed when the infant first stands and takes its first steps, returning with the advent of a mature gait at about 24 months of age.

The arm swing cannot be taken for granted, since it is lost in Parkinsonism when the stooped posture returns, but it is also lost or "buried" in the cocontraction of early bi-pedal mobility.

Wrap-Around Muscle Activation Patterns and Motor Development

Sutherland and colleagues (32) found prolonged calf muscle and tibialis anterior-muscle activation during gait in two-thirds of healthy 1-year olds and a third of typically developing healthy 7-year olds. This led to the observation of a "*wrap-around EMG*" pattern of muscle activation throughout the *stance* and *swing* phases of gait (32). This produces an ankle *equinus* pattern, i.e., plantarflexion in terminal swing causing the phenomenon of a tip-toe foot-contact pattern and of toe walking, so common in young infants, and contributing to the tottering, stiff-legged, high-energy, and unstable gait patterns typical of the "toddler" who is notoriously prone to frequent falls.

But as Sutherland discovered, one-third of healthy 7-year olds also exhibited this "wrap-around EMG" pattern of calf muscles leading to a phase of prolonged developmental toe walking (32). This developmental, non-pathological toe walking is conceptually important for our further understanding of pathological dystonia since, as will be demonstrated, it helps our understanding of how the motor system adapts to perturbations and injuries.

Developmental Cocontraction with Unfamiliar Tasks in Children and Teenagers

"Fog Posturing" assesses motor immaturity during unfamiliar tasks (33). All 4-year olds and 25% of 16-year olds exhibit involuntary associated postures of face, tongue, arms, or hands during unfamiliar tasks (33): a task-dependent "*overflow*" or dystonia persisting with learning difficulties, motor impairments, or speed of walking. The "Fog Manoeuver," i.e., asking the subject to walk on their toes, heels, lateral borders, and then the in-step of the feet, also accentuates the presence of latent or task-dependent coactivation patterns often referred to as "overflow." In the original Fog and Fog (33) report, asking children to open a bullfrog clip also produced associated, involuntary postures. *Of course the transition between a "developmental" overflow and "pathological" overflow is context-dependent, but the inability to suppress overflow at age-appropriate points must be considered part of a pathological spectrum of motor outputs that fall into the category of dystonias.* The Fog manoeuver may be used to accentuate subtle or latent dystonic postures in CP (34) or indeed isolated monogenic dystonias.

Selective Control (SC) and Surround Inhibition

Lack of selective motor control and surround inhibition in children with CP produces unwanted synergies (35).

Corticomuscular coherence amplitude is inversely related to motor performance in young adults but not modulated in young children and the elderly who have larger, more widely distributed cortical networks (36).

Magneto-encephalography, exploring cortico-oscillatory activity during knee extension tasks in CP children, demonstrated increased mean β-*event-related-desynchronization* (β-ERD) during motor planning but weaker γ-*event-related-synchronization* (γ-*ERS*) within primary motor cortex neurons (37).

A lack of selective motor control, excessive plasticity, and loss of surround inhibition is also a hallmark of dystonia (38, 39).

These observations raise important questions regarding the similarities and differences between these apparently different clinical groups.

One interpretation is that the young and elderly have less SC and reduced surround inhibition; a phenomenon shared with CP children and dystonic subjects.

AN UNMET NEED TO RECOGNIZE THAT DYSTONIA IS ABOLISHED BY SLEEP IN CHILDREN AND ADULTS AND MAY THEREFORE BE USED AS A DIAGNOSTIC CRITERION FOR DYSTONIA AS WELL AS THERAPEUTICALLY, FOR INSTANCE IN STATUS DYSTONICUS (SD)

One of the first questions a clinician should ask when faced with a child with a dystonic motor disorder should be:

1. "How are your child's movements and postures affected by sleep?"
2. "How much sleep is your child getting at night?"

The same questions can be raised when other colleagues refer children with motor disorders for further investigation and management.

The exploitation of sleep as a means of "switching off dystonia" is also an important therapeutic concept to be exploited in severe or life-threatening dystonias.

Dystonia and the Influence of Sleep

Dystonia is usually abolished by sleep and exacerbated by emotion, pain, mental concentration, or intention to move, i.e., by non-specific afferent inputs. Dystonia, Parkinsonian rigidity, tics, chorea, and athetosis are always abolished by sleep (40, 41). The exploration of the influence of sleep should therefore be a focus of all dystonia management plans (42–44) and may be considered the "*poor man's examination under anesthesia.*"

SD and Sleep

A crucial use of sleep to "switch off dystonia" in SD can be a very valuable clinical strategy for managing this life-threatening clinical catastrophe, which most commonly occurs in adolescent males with secondary dystonia, often of CP origin (42, 43, 45). The disadvantage of conventional muscle relaxants is that they also provoke respiratory depression and muscle weakness leading to central hypoventilation, shallow breathing, or frank apnoea (42, 43), whereas the hypnotic approach, e.g., with clonidine, can switch off SD by inducing sleep while preserving muscle function and breathing (43).

THE NEED TO RECOGNIZE DYSTONIA THAT PERVADES CP AND REVERSE THE OVER-INVESTMENT IN THE "SPASTIC MODEL" OF CP IN MEDICAL TEACHING AND TRAINING ON MOTOR DISORDERS IN CHILDHOOD ARISING FROM HISTORICAL ROOTS AT A TIME WHEN DYSTONIA WAS NOT COMMONLY RECOGNIZED LEADING TO AN UNDER-RECOGNITION OF THE TRUE PREVALENCE OF DYSTONIC CP INCLUDING A REEXAMINATION OF THE NATURE OF THE TONIC LABYRINTHINE RESPONSE (TLR)

Gowers' Description of Primary Spastic Paraplegia and the TLR and an Essentially Dystonic Phenomenology

Gowers produced one of the first clinical descriptions of a child with CP, which he attributed to pathology of the spinal cord arising during labour. This explains why this typical

description of CP in *A Manual of Diseases of the Nervous System* is found in *Volume 1: Diseases of the Spinal Cord and Nerves* with the two iconic illustrations Fig. 117, "*child seated*" and Fig. 118 "*child in supported standing*" (46), reproduced here in **Figure 2**.

Despite the repeated attribution of the clinical syndrome to "spastic paraplegia," Gowers' full description leaves little doubt that the features also include unequivocal descriptions of dystonia and chorea:

> The active contracture in the calf muscles, which most cases present, is a serious hindrance to walking even when the muscular power is sufficient. It is long before the attempt to walk overcomes the contracture. In most cases, however the child ultimately gains the power of walking, although much later than normal, and it often presents some peculiarity of gait, sometimes a tendency to "cross-legged progression" in which one foot gets over or in front of the other (Fig. 118), or a swinging oscillation of the body occurs which may persist to adult life. The infantile form may resemble very closely that which occurs in adults. There is the same extensor spasm and increase of all forms of reflex action. **As the child sits on the knee or a chair any sensory stimulus will make the legs shoot out in spasm (Fig. 117).** But the spasm does not reach the extreme degree often attained in the common form. The excess of the knee-jerk is always distinct, **but a foot-clonus is not often to be obtained**, perhaps because the muscle-reflex mechanism related to the calf-muscles has not received the functional development that must result from the ever-recurring sequence of tension and contraction involved in walking.

The frequent observation of dystonic choreoathetosis is explicitly described in Gowers' next sentences:

> The arms do not present tonic spasm such as is seen in adult cases. There may be choreioid disorder of movement, spontaneous irregular movements with inco-ordination. In the cases that can be fairly called "spastic paraplegia," the arm symptoms are slight. When considerable, the condition is usually termed "double athetosis" and its characters are described in diseases of the brain. [Gowers (46)]

The striking description of the "cross-legged progression" has been appropriated today as a hallmark of "spasticity," a concept, which unjustifiably pervades clinical practice, and serves to characterize the dominant phenotype of CP. But this peculiar cross-legged posture is seldom subjected to an operational analysis.

Gowers clearly describes sudden jerking extension of the legs precipitated by non-specific afferent inputs (i.e., increased arousal); there is seldom if any elicitable clonus at the ankle; the feet are maintained in an equinovarus posture; the published Fig. 117 (Vol. 1, p. 333) clearly shows spontaneous extensor great toes, a feature notable enough for the sketch drawn by Mr. H. R. Spencer to include this feature when drawn from the photograph taken by Mr. Hyde Marriott; the cross-legged posture occurs chiefly when the child is held in supported standing, i.e., head upright and again there are spontaneous extensor great toes in Fig. 118 (Vol. 1, p. 334). Finally Gowers explains: "*There may be choreioid disorder of movement, spontaneous irregular movements with inco-ordination.*"

This leaves little doubt that Gowers was describing a coexisting movement disorder, not just paralysis with brisk reflexes, and the

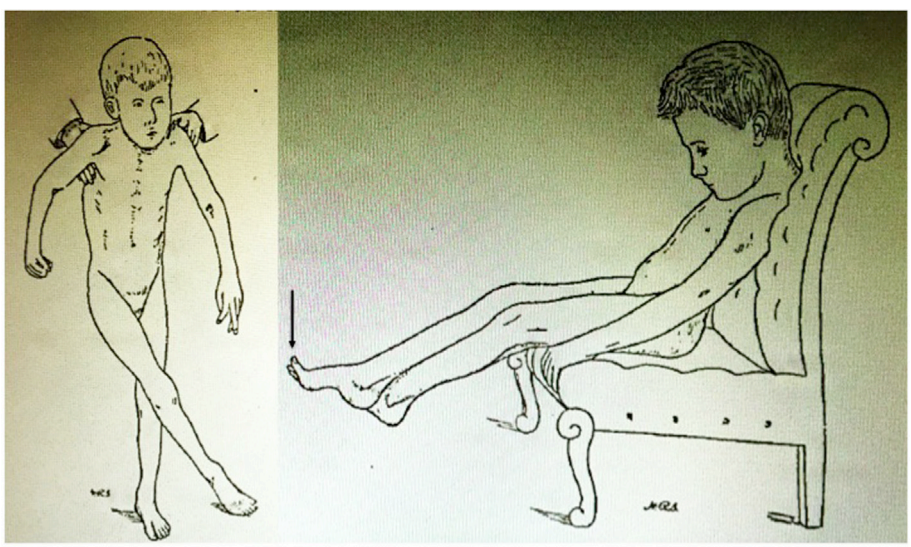

FIGURE 2 | Scissoring in cerebral palsy by Gowers (46).

appearance of this description under the section "Primary Spastic Paraplegia" must be considered misplaced.

This whole phenomenon has been reviewed under electromyographic recording (**Figure 3**) with specific attention to the following conditions:

Awake: in supine, decubitus, vertical suspension, and inverted suspension (**Figure 3**).

Awake and asleep in supine followed by waking up with EMG monitoring (**Figure 3**).

This careful observation demonstrates that the cross-legged posture of the legs is determined by arousal-wakefulness and exacerbated with increasing arousal-excitement. The cross-legged posture (now called "scissoring" of the legs) is completely inhibited by inverting the head and trunk, literally being held

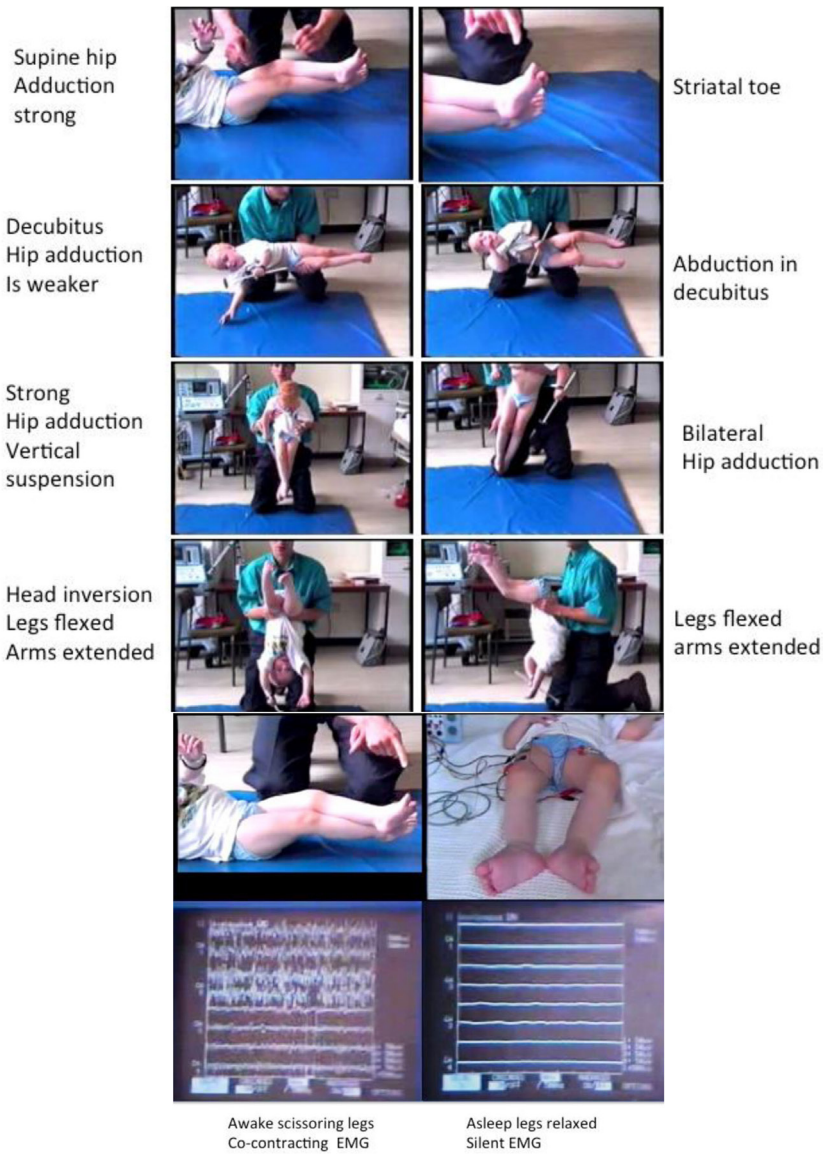

FIGURE 3 | **Tonic labyrinthine responses (TLRs)**. Provoked by supine and vertical suspension. Abolished body inversion (held upside down) and by sleep. Three-year old ex-preterm child with shunted hydrocephalus. See figures for explanation. The TLR is what produces "scissoring" in many children and young people with CP. Although often considered a feature of the "spastic syndrome," the TLR shares more in common with dystonia since it is associated with bilateral spontaneous extensor great toes also known as the "Striatal Toe" being a hallmark of dystonia. When the Babinski manoeuver is performed (stroking the sole of the foot firmly), the great toes flex. The TLR is also associated with cocontraction of agonist–antagonist muscles and this is abolished by sleep, another features of dystonia. *Operational definitions of the TLR*: Vertical suspension (top left) and supine lying (top right) bring out scissoring of the legs [adduction of the hips, extension of the knees, equinus foot posturing at the ankle, and spontaneous extensor (striatal) toes] (top panels). The legs cannot be passively separated (3rd panels from top) and move "*en bloc*." Inverting the child produces abduction and flexion at the hips with flexion of the knees and reduced ankle equinus (4th panels from top). Sleep abolishes the scissoring of the TLR in the supine posture (bottom left) and the muscles are completely at rest as measured by surface electromyography (bottom right): the legs are completely relaxed and offer no resistance to passive movements. *Adapted from Dr. J.-P. Lin "Motor Assessment in Children with Cerebral Palsy" Ph.D. thesis, 1998, Edinburgh*.

upside down, which also abolishes the tonic knee extension. This whole phenomenon being described by Denny-Brown (47, 48) and extensively reviewed by accessing the Denny-Brown collection of films (49).

Likewise the cross-legged posture, which is accompanied by spontaneous and continuous agonist–antagonist muscle contraction with the child in the awake, supine position (**Figure 3**) is also completely abolished by sleep, when the spontaneous EMG recordings cease altogether and the legs become completely flaccid at the hip and knee, ankle and externally rotated at the hip (**Figure 3**). Wakefulness-arousal immediately restores the scissoring leg posture (**Figure 3**).

None of the above-described phenomena are in any way related to the velocity-dependent increase in stretch reflexes described by Lance (50), the features being more consistent with a fixed dystonia (in contrast to rapid or phasic dystonia).

Responses to Postural Perturbation and the Dystonic Response

Another significant developmental milestone appears to be the ability to adaptively respond to sudden perturbations of posture. This was elegantly studied in typically developing children and children with CP by Nashner et al. (51) using tilt platforms to apply sudden forward or backward tilts.

When tilted forwards or backwards, healthy children stabilize the ankle followed by the knee joint later: a "*distal-to-proximal*" muscle activation. In hemiplegic or diplegic CP "*proximal-to-distal*" activation sequences occur when tilted forwards or backwards, except in *uninvolved* legs of hemiplegic or ataxic children (51, 52) Nashner concluded:

> The results of moving platform assessment support the contention that pathological changes in stretch reflex mechanisms associated with spasticity are secondary to the primary functional loss: namely, alterations in central and spinal programs which impose the appropriate temporal and spatial structures upon motor activities of the limb prior to the execution of the task (51).

Nashner is categorical: the response to perturbation in CP children is a maladaptive proximal to distal motor-activation ripple which acts first in muscles around the hip, momentarily leaving the knee and ankle relatively flail. This contrasts with the strategy of stabilizing ankle and knee joints before stabilizing the hip joint in healthy children. Inputs from the labyrinths (vestibular system) facilitate functional postures but are exaggerated in "*quadriplegia*" and "*diplegia*" according to head position.

Dystonia, rigidity, chorea, and hemiballismus reflect imbalances between desired and competing cerebello-thalamo-cortical-basal ganglia circuit activity causing a failure to inhibit unwanted movements through abnormal activation patterns of groups of striatal neurons (53, 54) within segregated and integrative connectivity patterns in the human basal ganglia (55). Posterior sensorimotor, middle cognitive–associative, and anterior limbic functions being respectively colocated in each basal ganglia structure (55). Understanding how we develop *habitual* as opposed to *goal-directed movements* (27) could explain why children with CP have difficulty producing successful habitual motor repertoires.

A NEED TO RECOGNIZE THAT MANY DIFFERENT PATTERNS OF BRAIN INJURY CAN CAUSE DYSTONIA: EMPHASIZING DYSTONIA AS A MANIFESTATION OF A DISTURBED DISTRIBUTED NETWORK

If we accept that dystonia emerges out of an initial developmental cocontraction pattern of movements and postures and that motor development arises from an *ab initio* hyperkinetic motor condition, it is not difficult to understand why so many disorders with seemingly completely different mechanisms result in dystonia.

Apart from the classical injuries of the developing brain (56), approximately 17–20% of children with CP have normal neuroimaging (57–59), which calls into question "*where exactly is the non-progressive injury to the developing brain*" said to be the defining hallmark of CP? A feature all the more intriguing when over 50% of children with "dyskinetic CP" have normal brain imaging (60).

This suggests that the brain in early dystonic motor disorders may fail to develop the efficient and functional connectivity networks underpinning normal motor development. By extension of this hypothesis, the child with early onset dystonia may be utilizing an under-pruned, over-arborized network of connections (rather than a damaged network). This calls into question therapeutic approaches centered on "curing" CP with stem cell therapies, for instance see Graham (44) for a recent discussion of the role of stem cells in CP. However, it is conceivable that stem cells, not only repair damaged areas of the brain but also facilitate activity-dependent plasticity, which could be associated with promoting functional connectivity.

Connectivity within the brain of the child with dystonia, may be measured by whole white matter fractional anisotropy (FA) estimations using diffusion-weighted imaging methods with the technique of MRI Diffusion Tensor Imaging. This provides information about white matter microstructure integrity and is derived from the differential diffusion of water molecules along fiber tracts. The FA value from 0.0 to 1.0 represents the likelihood of water diffusing along fibers (FA maximum = 1.0) or water diffusing randomly in all directions because there are no fibers (FA minimum = 0.0). The FA value may therefore be a useful marker of the connectivity of the brain: higher FA values corresponding to greater structural connectivity and integrity of the white matter fiber tracts within the brain and *vice versa*. For instance, in a cohort of children selected on clinical, conventional radiological, and neurophysiological assessments (61, 62) preparatory to management of dystonia with DBS or ITB, the mean DBS-group FA value was >0.5, but the FA value was <0.5 in the ITB group (63). Such statistical imaging parameters may in the future, with neurophysiological parameters become a means of appropriately stratifying children with dystonia into prognostic groups suitable for intervention with DBS or ITB.

THE NEED TO RECOGNIZE NON-MOTOR SYMPTOMS IN CHILDHOOD DYSTONIA

The focus on the classic motor symptoms of dystonia, i.e., involuntary muscle contractions and abnormal postures has left a gap in research on the non-motor aspects of the dystonic disorders such as abnormalities in sensory and perceptual functions, neuropsychiatric disturbances, and sleep. The comorbidity of non-motor symptoms is increasingly recognized in adults with dystonia (64, 65). It is not known, if these non-motor symptoms, including poor sleep patterns (41), are intrinsic to dystonia comorbidities or secondary to the dystonia disorders themselves. Understanding the role of non-motor symptoms in childhood dystonia has potential implications for clinical assessment tools; pre- and post-surgical interventions, e.g., deep brain stimulation (DBS), and treatment targets. Moreover, these non-motor symptoms play a vital role in determining quality of life. Although research has begun to investigate these non-motor phenomena in typically developing children and autistic children, no systematic evaluation of non-motor symptoms exist for the childhood dystonia population.

A recent comparison of the relationship between Burke Fahn Marsden Dystonia Rating Scale-motor (BFMDRS-m: measuring dystonia severity) and three functional measures, the Gross Motor Function Classification System (GMFCS), the Manual Abilities Classification System (MACS) and Communication Function Classification System (CFCS) showed an extremely good linear correlation between the BFMDRS-m and the GMFCS, indicating an approximately 20–25 absolute BFMDRS points between each of the five divisions of the GMFCS (Grade I = athletic, Grade V = no mobility at all). However, although the BFMDRS-m correlated well with the MACS, the BFMDRS did not discriminate well between Grades I, II, and III of the five MACS grades, suggesting that non-dystonic variables also impair manual abilities: e.g., processing skills or lack of opportunity to practice skills (66).

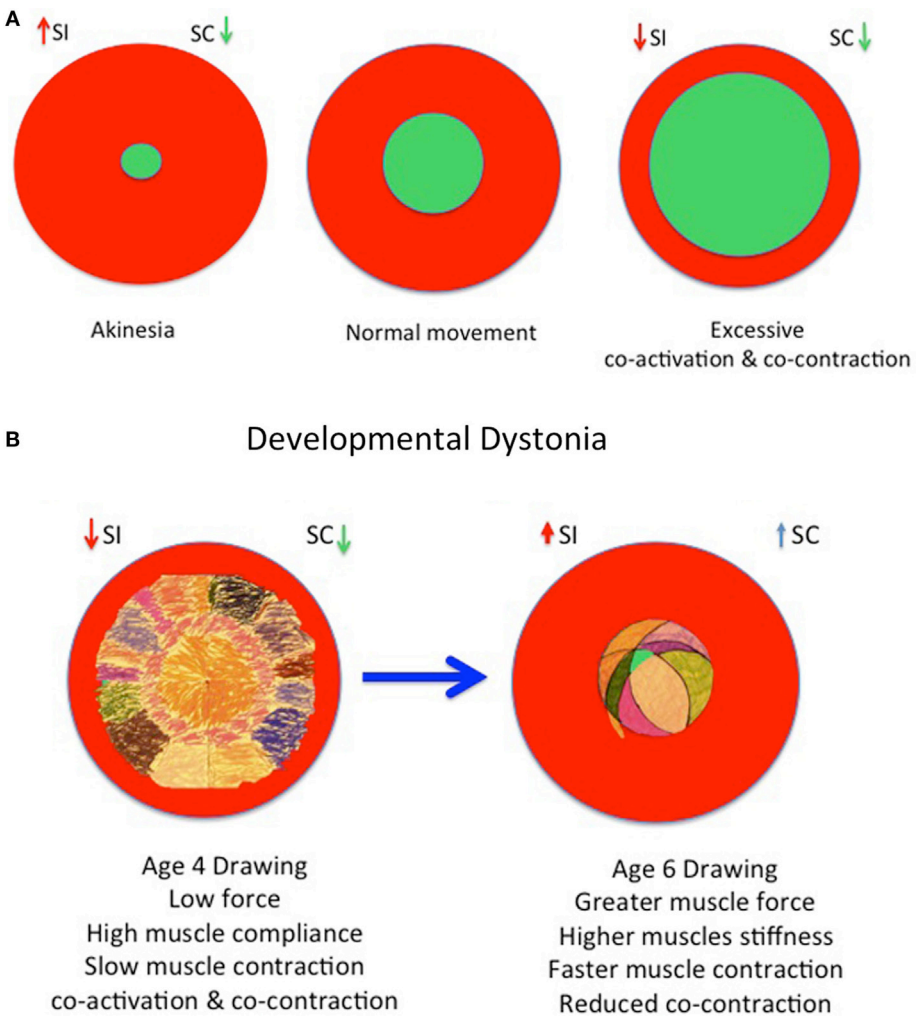

FIGURE 4 | Developmental model of physiological and pathological dystonia in young and elderly.

(Continued)

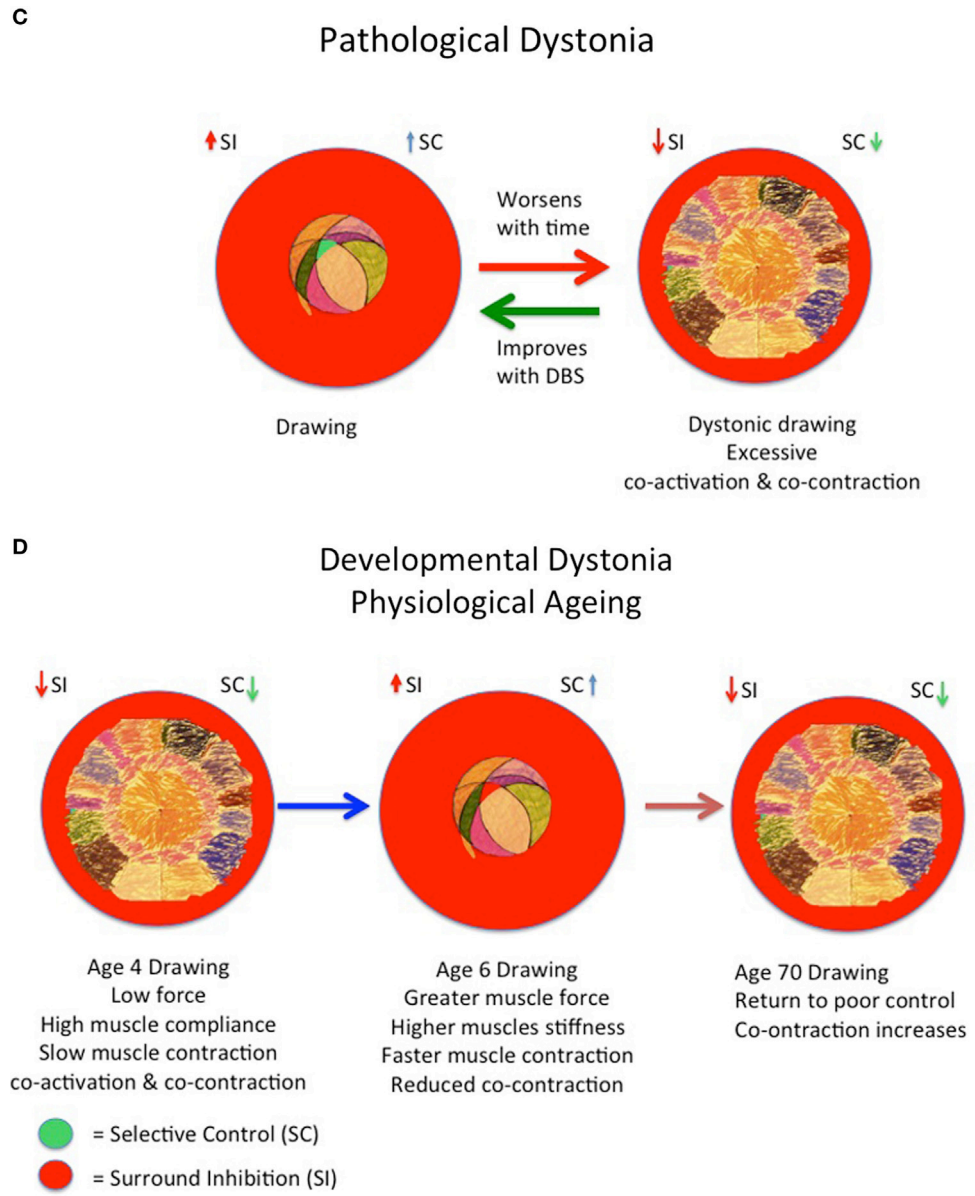

FIGURE 4 | **Continued**
(A) Model of akinesia, kinesia, and hyperkinesia according to relative balance of selective control (SC) and surround inhibition (SI) with rise in cocontraction. **(B)** Increasing SC as increasing surround inhibition (SI) "prunes" excessive movements in childhood from age 3 to 6 years, respectively. **(C)** The onset of pathological dystonia is associated with reduced surround inhibition (SI) and reduced SC. **(D)** The elderly experience reduced SC and reduced surround inhibition (SI) with consequent loss of skilled performance. Adapted from Lin et al. (30), Mink (53), Tedroff et al. (35), and Graziaido et al. (36).

Further work on the non-motor aspects of living with dystonia is urgently required. These non-motor aspects of dystonia could relate to abnormal sensory processing, body image, cognitive issues, and the social context of physical dependency and lack of opportunity for independence.

Additional areas for exploration in dystonia include the role of mirror neurons and the ability or otherwise to learn new motor skills through observed movements when living and growing as a child with dystonia.

MEASURING WHAT MATTERS MOST TO CHILDREN WITH DYSTONIA IS ALSO AN UNMET NEED

Most studies fail to report what matters most to children with dystonia and their carers: reduction in pain, improvements in activities of daily living, and manual function (67, 68). This is a particularly important failing since dystonia worsens in approximately 2/3 of cases and remains severe in a further 1/3

of cases referred for further management after conventional medication (1).

THE UNMET NEED OF PREVENTING DEFORMITY IN CHILDHOOD DYSTONIA

Fixed musculoskeletal deformity (FMD) appears inexorably with each successive 5 years of living with dystonia in children but is most marked in the secondary dystonias (69). For instance the median age of FMD in primary dystonia is >21 years (95% CI: 16–21 years) but falls to 6 years (95% CI: 5.0–6.1 years) in secondary dystonias, and 7.4 years (95% CI: 4.4–10.4 years) in heredodegenerative dystonias.

Urgent means are required to forestall the onset of deformity in childhood secondary dystonia, particularly in CP children with a GMFCS level V, since secondary dystonias are very vulnerable to early fixed deformity, certainly before the age of five and well before the end of primary school education (69).

EXPLORATION OF BETTER PHARMACOLOGICAL APPROACHES TO MANAGING DYSTONIA IN CHILDHOOD AS AN UNMET NEED

Although several medications are regularly used in the first-line management of dystonia, the evidence to support pharmacological agents in childhood dystonia is weak (70). Trihexyphenidyl has some evidence of efficacy to support its use in adults with dystonia. In a retrospective cohort of 278 children with dystonia referred to a single center from all over the United Kingdom and Republic of Ireland, medication use had been prospectively gathered including adverse drug reactions (ADR) (71).

The commonest drugs used were baclofen (118/278: 42.4%), trihexyphenidyl (98/278: 35.2%), L-dopa (57/278: 20.5%), and diazepam (53/278: 19%). Choice of medication appeared to be influenced by dystonia etiology (71). ADR had occurred in 171/278 (61.5%) of children: the commonest drugs responsible for ADR being trihexyphenidyl (90/171: 52.3%), baclofen (43/171: 25.1%), and L-dopa (26/171: 15.2%) (70). Unfortunately, pharmacological management of dystonia in children is often disappointing or not tolerated (70, 71). No medication is licensed for the management of dystonia in childhood (70). This includes new conceptual approaches to mechanisms of relieving dystonia. Gabapentin has been reported to be beneficial in relieving dystonia in a relatively large open trial in children with often severe dystonia, which was liable to disrupt night sleep, impair the capacity to tolerate sitting comfortably, reduce activities of daily living, disrupt mood and behavior, and very often associated with severe pain (72). Outcomes were measured using the Dystonia Severity Assessment Plan (DSAP) (42) and the activities of daily living were mapped on a scale of 0–4 using the WHO International Classification of Function where 0 = no difficulty and 4 = maximum difficulty most of the time (72). Gabapentin may thus become a new, "*re-purposed*" medication for routine management of dystonias in childhood subject to further studies with a view to obtaining a license for gabapentin liquid and tablets/capsules in childhood dystonia.

THE NEED TO ADEQUATELY MANAGE LIFE-THREATENING DYSTONIAS IN CHILDHOOD INCLUDING "BRITTLE DYSTONIA" AND SD

In a recent study of over 50 cases of SD in children and young people, SD was reported to be life-threatening in up to 10% of cases (45) from multi-organ failure but also because the use of muscle relaxants such a benzodiazepine infusions and high-dose baclofen can cause respiratory depression.

The use of a scale such as the DSAP (42, 43, 72) may help measure change and recovery together with drug and therapeutic efficacy, by promoting sleep as a major strategy for switching off dystonia rather than resorting to muscle relaxants and ventilator support. The importance of the sleep chart must be emphasized in monitoring the well being of those children with dystonia who are liable to experience frequent episodes of severe dystonia (brittle dystonia) requiring hospital admission often in high-dependency units or pediatric intensive care units.

Early features of decompensating dystonia may be detected using the DSAP. DSAP Grade I = sitting comfortably all day; Grade II = unable to tolerate sitting; Grade III = unable to sleep at night; Grade IV = early metabolic decompensation, sweating, and mild rhabdomyolysis; and Grade V = full SD with multi-organ failure. The change in DSAP can prompt seeking advice and intervention before dystonia decompensation, as well as a means of monitoring progress toward recovery. DBS now has an important role in the management of SD (43, 45).

THERE IS AN UNMET NEED TO DEVELOP GOOD BIOMARKERS FOR DYSTONIA IN CHILDHOOD

We have already looked at non-invasive neurophysiological variables throughout this review, most of which will depend on clear operational definitions for measurement and interpretation of clinical significance. Such measures lead to categorical and quantitative data, e.g., the latency of central motor conduction times (61, 62). White matter integrity as measured by the FA value (62, 63) may be used to partition cases most likely to benefit from DBS or ITB (63) and thereby improve the prognosis for a favorable outcome from DBS for dystonia along with somatosensory-evoked potentials (SSEP) (J-P Lin unpublished results).

Other imaging modalities, such as 18-fluorodeoxy Glucose Positron Emission Tomography (FDG-PET-CT) imaging, may also permit individual and group analyses of cerebral function in dystonia using statistical parametric mapping techniques which may shed light on how dystonia affects brain function and highlight differences between different causes of dystonia such as between primary dystonia and dystonia arising from neurodegeneration with brain iron accumulation (NBIA) caused by the pantothenate kinase-2 (PANK-2) mutation (73). Other

dystonias may reveal other resting state glucose metabolism patterns reflecting functional connectivity patterns in children with and without conspicuous brain injuries (Lin, unpublished observations).

More invasive studies, such as globus pallidus internus microelectrode recordings (GPIMER) have revealed differences in the proportion of irregular and bursting cells in children undergoing DBS for dystonia (74). Children suffering from NBIA, mostly secondary to PANK-2 disease had mostly regular GPI neuronal firing patterns and the highest mean GPIMER neuronal instantaneous firing frequencies, with no bursting cells. In contrast, the secondary dystonias had the slowest mean and median GPIMER instantaneous firing frequencies, but the same relative proportion of bursting cells as primary dystonias (74). In addition, the GPIMER for postneonatal secondary dystonias had higher instantaneous firing frequencies than found in the GPIMER firing frequencies in children with perinatal causes of dystonia. Such GPIMER firing frequencies correlated positively with follow-up changes in the BFMDRS at 1 year after DBS surgery (74).

AN UNMET NEED FOR RAPID DIAGNOSTIC TESTING IN CHILDHOOD DYSTONIAS AND EARLY RECOGNITION OF CHILDHOOD-ONSET DYSTONIA

Next generation DNA sequencing should reduce the wait for molecular confirmation of a genetically inherited movement disorder, including the dystonias. Currently, the clinical reality is that there are huge time-lapses between the clinical suspicion of a genetic basis to dystonia and genetic confirmation. This lack of clarity delays clinical decision-making and sustains the anxiety surrounding every "unsolved" case of dystonia. The possible overlap between the genetic dystonias and a possible perinatal mechanism is especially likely when brain imaging is unremarkable.

Another diagnostic dilemma is the advent of multiple clinical phenotypes arising from a single genetic disorder, a phenomenon known as phenotypic pleiotropy, which may present, for instance, as seizures in infancy and a movement disorder many years later.

Genetic heterogeneity and phenotypic pleiotropy have further supported the case for a basic neurogenetic screen in children with neurological disorders (75), even in those children in whom there appear to be brain scan imaging changes and particularly in those CP cases with apparently "normal" brain scans.

Such a widespread screen would identify more genetic cases and broaden our phenotypic understanding of gene functioning and aid population modeling of dystonic disorders in childhood.

Dystonia in children often requires time to be recognized, assessed, and eventually diagnosed, perhaps not surprisingly, given the immense neurodevelopmental backdrop of cocontraction underpinning early human motor patterns.

With regard to clinical presentation, the typical site of onset of childhood isolated dystonia is in the lower limbs; a considerable proportion of cases subsequently generalize to involve the trunk and upper limbs, while onset in the cervical, oromandibular, and laryngeal regions are less frequently encountered and should always lead to ruling out secondary causes of dystonia, such as NBIA, cerebral neoplasia, or disorders of the cranio-cervical junction.

Abnormal postures of the ankle, foot or both, or an abnormal gait pattern due to mobile lower limb dystonia can take a long time to be recognized as a primarily neurological issue. In this regard, there is an unmet need to bridge the gaps between orthopedics and neurology, thus widening the knowledge and awareness by other professionals of childhood dystonia. This may hopefully allow children to be promptly assessed by child neurologists and referred to dedicated movement disorders clinics.

Early clinical diagnosis not only leads to early management but also to early counseling to patients' families. Children affected by dystonia are mostly sporadic cases, namely no additional family members are affected and their parents are healthy. A recurrent question made by children's families in pediatric movement disorders clinics is about the probability of other children being affected by the same disorder. This question still remains unanswered in many cases; in fact, it is impossible to estimate the risk of transmission of these dystonias to offspring without a definite genetic diagnosis in the proband. Recent advances in genetic techniques have allowed the recognition of an increasing number of genes underlying dystonia, but most of the genes discovered in the past 4 years seem to be almost exclusively found in adult-onset cases (e.g., GNAL, ANO-3) and are apparently a very rare cause of dystonia. For example, only 53 patients with GNAL mutations have been reported since the discovery of this gene in 2012 (76), and only 10 ANO-3 positive patients have been fully characterized clinically (77). Moreover, no dedicated studies aimed at assessing the frequency of mutations in these genes have been performed in pediatric cohorts of patients. Thus, there is a current unmet need to better characterize the genetic causes of dystonia in children by analyzing not only well known genes such as DYT-1 and DYT-5 but also recently discovered genes that have primarily been characterized in adult patients, or which exhibit phenotypic pleiotropy on the one hand (75), and to account for the growing recognition of genetic heterogeneity in the causes of dystonia on the other (75). This is ideally possible by using next generation sequencing platforms containing all the dystonia-related genes reported so far, but even by using this powerful tool, a significant proportion of pediatric patients still remain genetically undiagnosed. This reinforces the hypothesis that dystonia is a complex and genetically heterogeneous disorder and additional efforts are needed to share patients' DNA samples among research centers to discover new dystonia-causing genes. The availability of genetic tests in clinical practice will be crucial to widen our knowledge of dystonia, clinical phenotypes, and disease course in affected patients. However, the rising number of new gene discoveries and the movement disorders they may cause provide a formidable task for even specialist clinicians to keep up with (78), even though genetic experts are doing their best to provide rational systems of movement disorder gene classifications (79).

DEVELOPING COHERENT, NETWORKED RESEARCH STRATEGIES FOR DIAGNOSING AND STRATIFIED MANAGEMENT OF DYSTONIAS IN CHILDHOOD: AN UNMET NEED

It is not enough to focus on very specific, mostly rare, and monogenic dystonias. Another approach, as described in this text, is to look at the shared characteristics of all childhood dystonias to find techniques that can ameliorate the lives of children, especially with early-onset dystonias. This approach requires a more thorough analysis of the stages of motor development, including key elements underpinning human motor development and function susceptible to *disruption*, *suppression* or *arrest* by uncontrolled early dystonia.

Monogenic isolated dystonias, dystonia plus, and even progressive dystonias often have a period of normal early motor development which offers the possibility that functional skills may return more easily and quickly if dystonia can be reduced, for instance with neuromodulation by DBS. Conversely, this is less likely to occur in the absence of an early period of normal motor development before dystonia-onset, as is typical of isolated or mixed secondary dystonias such as dystonic CP (1). This leads us to consider a paradox: dystonia may be considered to be a product of excessive neuronal plasticity and inadequate surround inhibition (38, 39). But cases that become DBS-dependent, often requiring high DBS currents to maintain dystonia suppression, are said to possess too little cerebral plasticity to produce long-lasting "DBS-off" dystonia suppression (80, 81). We thus need to understand how cerebral plasticity; long-term potentiation and long-term depression can be harnessed or focused in all these different childhood dystonias.

An additional factor is the burden of growing and developing with continuously disruptive dystonic movements and postures leading to a concern that the "proportion of life lived with dystonia" (dystonia duration/age) can adversely compromise future motor skill acquisition and reduce the neuromodulation efficacy of interventions such as DBS through lost opportunities for activity and participation (1) since living with dystonia for a long time may reduce the likelihood of reducing dystonia (82).

Dystonia in childhood remains largely a physiological mystery, all the more complex because it occurs in the context of a developing brain. A number of theoretical approaches have been advanced to understand how dystonia and other early-expressed neurological disorders can be understood. These include the neuronal group selection theory proposed by Hadders-Algra (83), which attempts to model how groups of neurons within a network establish patterns of behavior. But neurodevelopmental therapy, in the form of Sensory Integration, the dominantly promoted management for motor disorders in children since the 1970s, has not proven beneficial when closely evaluated (84).

A recent review of a framework for understanding many different early onset neurodevelopmental disorders examines the "critical" and "sensitive" windows of brain plasticity that depend on expected inputs during "critical periods" which may be disrupted by other inputs during later "sensitive periods" when programed developmental outcomes are thwarted by neurological disorders (85). For instance, the visual cortex expects visual inputs in a critical period, which if missed, leads to visual agnosia, e.g., ocular defects may produce amblyopia in uncorrected squints. However, auditory and tactile stimuli may have greater cortical representation and help compensate for the blindness. Similarly, the auditory cortex requires early auditory inputs to develop language. Congenital deafness must be corrected early, e.g., within 5 years of life but typically as early as possible if the child is to develop language skills (86, 87).

Developmental dystonias and epilepsies take their toll on the developing brain by subverting this delicate plastic organization, which require timely interventions that can restore functional adaptive plasticity.

Collaborative networks are required using common definitions and meaningful outcome measures to develop adequate dystonia stratification for therapeutic choice and individual patient prognosis (88, 89) within a framework of the International Classification of Function (90) with measures that are meaningful to children with dystonia and their families (66–68). New work is differentiating the relative impact of dystonia on function compared to choreoathetosis and this reveals that dystonia is the most important factor associated with neurodisability (91). These studies must be augmented with new, clinically relevant studies to help parents and carers, children, and young people make appropriate decisions in relation to complex neurosurgical interventions such as DBS (where appropriate) (92–95). But for any field to prosper we must be prepared to look elsewhere for examples of success and also applications of successful neuromodulation interventions, for instance, in the management of chronic pain (96) and bladder and bowel incontinence (97) where neuromodulation can make a significant positive impact. We must also evaluate the childhood brain and define stimulation targets in appropriate targets of the motor conectome in children (98) and ensure preservation of cognitive (99) function and accept the technical challenges of new imaging techniques to safely work with neuromodulation systems (100).

In implementing new technologies we must take care to integrate these within a framework of close cooperation with children, families, carers, and colleagues, using "the broad clinical gaze" which avoids a merely technocratic solution by working in the best interests of the child (101). A major approach advocated in this manifesto, is to study what all dystonias share in common since this must represent what is biologically fundamental to the dystonic state. Such an approach may produce surprising and novel ways of dealing with the current "unmet needs in dystonia." This "manifesto" should stimulate and facilitate clinical networking, appropriate diagnostic "stratification" and functional assessments for precision medical and functional neurosurgical intervention selection and research in childhood dystonias.

ETHICS STATEMENT

Photographs of clinical demonstrations relating to physiology of the TLR were performed by J-PL as part of his Ph.D. thesis "Motor Assessments in Cerebral Palsy" at the Royal Hospital For Sick

Children, Edinburgh and were granted approval by the Lothian and Borders Health Board Research and Ethics committee. Pediatric/Reproductive Medicine Ethic of Medical Research subcommittee: Protocol 10/92: "The objective assessment of muscle tone, posture and movement in cerebral palsy" 16.09.92 (ref CJA/JHNL). Other clinical photographs are published with clinical consent within Guy's and St Thomas' NHDS Foundation Trust.

AUTHOR CONTRIBUTIONS

J-PL conceived the project, wrote the first draft, added some clinical examples as demonstrations, and critically reviewed the manuscript. NN critically reviewed the manuscript.

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APPENDIX

Panel 1. A Manifesto of Unmet Needs in Isolated Childhood Dystonias

The following headings represent some of the unmet needs in understanding and managing childhood dystonia:

1. There is a need to recognize the importance of early experience of movement for the fetus and infant and environmental effects on this early development.
2. A need to recognize the link between childhood dystonias and patterns of movement and postures in the infant and toddler. This involves recognizing the key patterns of emergent motor development and applying operational definitions that enable recognition of these key patterns, including understanding the link between developmental dystonia and pathological dystonia at all ages of life.
3. An unmet need to recognize the similarities and differences between developmental cocontraction, task-dependent cocontraction, the pathological cocontraction of dystonia, observations of selective motor control, and surround inhibition in children, the elderly, and in dystonic individuals.
4. An unmet need to recognize that dystonia is abolished by sleep in children and adults and may therefore be used as a diagnostic criterion for dystonia as well as therapeutically, for instance in status dystonicus.
5. The need to recognize dystonia which pervades cerebral palsy and reverse the over-investment in the "spastic model" of cerebral palsy in medical teaching and training on motor disorders in childhood arising from historical roots at a time when dystonia was not commonly recognized leading to an under-recognition of the true prevalence of dystonic cerebral palsy including a reexamination of the nature of the TLR.
6. A need to recognize that many different patterns of brain injury can cause dystonia: emphasizing dystonia as a manifestation of a disturbed distributed network.
7. The need to recognize non-motor symptoms in childhood dystonia.
8. Measuring what matters most to children with dystonia is also an unmet need.
9. The unmet need of preventing deformity in childhood dystonia.
10. Exploration of better pharmacological approaches to managing dystonia in childhood as an unmet need.
11. The need to adequately manage life-threatening dystonias in childhood including "brittle dystonia" and status dystonicus.
12. There is an unmet need to develop good biomarkers for dystonia in childhood.
13. An unmet need for rapid diagnostic testing in childhood dystonias is the need for an early recognition of childhood-onset dystonia.
14. Developing coherent, networked research strategies for diagnosing, and stratified management of dystonias in childhood: is an unmet need.

Panel 2. Dystonia, Dyskinesia, and Hypertonus

> Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Dystonia is classified along two axes: clinical characteristics, including age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features), and etiology, which includes nervous system pathology and inheritance. The clinical characteristics fall into several specific dystonia syndromes that help to guide diagnosis and treatment.
>
> Albanese et al. (102)

The terms Dyskinesia and Hypertonus occur throughout the literature on CP and have overlapping but also distinct meanings

Dyskinesia

"*Dyskinesia*" or "dyskinetic" is a term originating from the Surveillance of Cerebral Palsy in Europe collaboration and has been used in many studies on CP which encompasses non-spastic and non-ataxic features including cases of *dystonia* or choreoathetosis in isolation or both in varying proportions. The term "*dyskinetic cerebral* palsy" implies CP dominated by *dystonia*, *choreoathetosis*, or both (103).

Hypertonus

The *Task Force on Childhood Motor Disorders*[104] is a North American consortium which uses the term "*hypertonus*" as a collective term for disorders of tone which requires further subdivision into "*spasticity*," "*dystonia*" and "*rigidity*":

"Spasticity" is defined as hypertonia in which 1 or both of the following signs are present:

(1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or
(2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle.

"Dystonia" is defined as a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.

"Rigidity" is defined as hypertonia in which all of the following are true (104):

(1) The resistance to externally imposed joint movement is present at very low speeds of movement, does not depend on imposed speed and does not exhibit a speed or angle threshold;

(2) Simultaneous cocontraction of agonists and antagonists may occur, and this is reflected in an immediate resistance to a reversal of the direction of movement about a joint;
(3) the limb does not tend to return toward a particular fixed posture or extreme joint angle; and
(4) voluntary activity in distant muscle groups does not lead to involuntary movements about the rigid joints, although rigidity may worsen.

Panel 3. Causes of Cocontraction in Children

(a) Developmental cocontraction.
- Fetal and early postnatal postures.
- High muscle–tendon compliance.
- Slow muscle contraction and relaxation characteristics.
- Weak force generation.
- Reciprocal excitation due to co-innervation of agonist–antagonist pairs.
- "wrap-around" muscle activation in gait cycle of infants and young children.
- Joint-synchronies: e.g., triple-flexion hip, knee, and ankle joints till age 2 years.
- Developmental crouch posture of infant and toddler.
- Fog posturing performing unfamiliar tasks: all 4-year olds and 25% 16-year olds when asked to walk on toes, heels, lateral border, and in-step of feet.
- Corticomuscular coherence amplitude modultion[1]: Reduced in the children and elderly and linked to greater cortical recruitment for everyday tasks.

(b) Task-dependent cocontraction.
- Increasing walking speed leads to cocontraction.
  - Children with bilateral CP tend to hurry when walking thus exhibiting more task-dependent cocontraction.

(c) Pathological cocontraction.
- Dystonia:
  - Associated with "reduced surround inhibition" and "increased plasticity" (see text footnote 1).
  - Dystonia is abolished by sleep (see **Figure 3**).
- Pathological crouch posture.
- Involuntary synergies during voluntary tasks (see text footnote 1):
  - Increased mean β-ERD.
  - Reduced γ-event-related synchronization.

(d) Tonic labyrinthine postures.
- Alterations of position of head in space produces cocontraction which is abolished by sleep (see **Figure 3**).

[1]Note reduced surround inhibition leading to excessive motor synergies/cocontraction during motor tasks (see **Figures 4A–D**). There are similarities between motor findings in the young, the elderly (see **Figure 4D**), dystonic individuals, and CP children (see **Figure 4C**).

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Needs and Requirements of Modern Biobanks on the Example of Dystonia Syndromes

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Dystonia belongs to a group of rare diseases (RDs) characterized by etiologic heterogeneity, affection often in childhood, severe and variable clinical manifestation. The burden of this disease is aggravated by the lack of effective and specific treatment. In the field of dystonia as in other RDs the number of available biospecimens is, in general, limited. Here, we report a new approach to collect clinical and genetic data in biospecimens maintained collaboratively by researchers and their associated institutions in a decentralized system. Allowing researchers to have access to significant numbers of samples and corresponding clinical data, biobanking in dystonia might not only provide a powerful tool in the identification of disease genes but also the classification of variants detected in known genes with respect to their clinical relevance. Growing data in genetics due to the technical progress demand for well-annotated and well-managed biobanks, which in near future hold even the potential for biomarker research and generating medical treatment based on clinical and genetic data currently summarized as "personalized medicine."

Keywords: biobank, rare disease, dystonia, genes, Euro-dystonia

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INTRODUCTION

Rare diseases (RDs), also called orphan diseases, of which there are approximately 5.000–8.000, are diseases that affect a small number of people compared to the general population, and specific issues are raised in relation to their rarity. They are often genetic in origin (1, 2). Specific challenges for health care and for research are the rarity and the heterogeneity of RDs. These also affect the development of therapies and their marketing. As a result, many patients with RDs do not receive a timely and accurate diagnosis (3, 4), have to consult numerous doctors to obtain a final diagnosis, and only few receive tailored treatment influencing survival and/or quality of life. It is because of these specific challenges that the EU Public Health Programme 2008–2013 has made RDs a priority area for action. A large number of RD-focused projects have been selected for under the Sixth and Seventh Framework Research Programmes (5). More recently, a proportion of Horizon 2020, one of the largest EU Research and Innovation programmes with a budget of almost 80 million Euro, is specifically aimed at RD initiatives (6). Experts now hope that on the basis of their genetic knowledge and pathway definition, they will be able to develop a new concept, often called "precision medicine." This should change our view on how to apply therapeutic targets. Collecting clinical and genetic data

and also biospecimens (biobanks) will become more important in the diagnosis and therapy development for RDs.

To look for an example of a RD, we should look at dystonia. Dystonia is a hyperkinetic movement disorder and is characterized by sustained muscle contractions with repetitive movements and also abnormal postures. It is difficult to establish specific information on the prevalence of dystonia because of the lack of a representative number of population-based studies. However, based on the current data, the overall prevalence of "primary" dystonia, an umbrella term describing a number of familial and sporadic forms of the disease, is calculated at 16.43 per 100,000 (95% confidence interval: 12.09–22.32) (7).

In this article, our aim is to review the current situation and future direction of RD biobanks by looking at examples of dystonic syndromes and discussing the research and development arising from the use of biospecimens, so as to improve the disease management.

DEFINITION OF THE RARE DISEASES DYSTONIA

Rare diseases can manifest at any stage in life, though generalized or severe forms often start in early childhood. Common RD characteristics are genetic, severe, disabling, non-preventable, sometimes fatal, progressive, and having no specific effective treatments (8, 9). Recently, the Australian rare disease community proposed a definition for RD as being "a life-threatening or chronically debilitating disease which is statistically rare, (with an estimated prevalence of less than 1 in 2,000 or of similarly low prevalence) and has a high level of complexity such that special combined efforts are needed to address the disorder or condition" (10).

Dystonia, a good example of a RD, meets this definition, even if it does not describe a specific disease or pathomechanism. Dystonia is a general term for a large group of movement disorders. These may vary in their symptoms, their causes, their progression, and their treatments (**Table 1**). Dystonia generally shows sustained or intermittent muscle contractions. These can cause abnormal and often repetitive movements and postures. Dystonic movements will often be patterned and twisting, may be tremulous, affecting the neck, the torso, the limbs, the eyes, the face, the vocal chords, and even a combination of these muscle groups. Dystonia can be initiated and worsened by voluntary action and is associated with overflow muscle activation (11). Dystonic postures may cause varying degrees of pain and disability. These can range from occasional and mild symptoms to severe, debilitating symptoms, significantly affecting a person's quality of life. Dystonia can become progressively worse but remains unchanged in some cases. In rare cases, it has been known to spontaneously remit. Treatment will depend on several factors, e.g., specific subtype and can include medication, botulinum toxin injections, physical therapy, or even surgery.

TABLE 1 | Examples for dystonic syndromes.

Blepharospasm
Writer's cramp
Spasmodic dysphonia
Cervical dystonia
Oromandibular dystonia
Meige syndrome
Myoclonic dystonia
Generalized dystonia
Rapid-onset dystonia-parkinsonism
Paroxysmal kinesigenic dystonia
Paroxysmal dystonia choreoathetosis
DOPA-responsive dystonia
Tardive dystonia

Although various elements can contribute to the development of dystonia, in many cases, the exact, underlying causes are unknown. Despite the etiological heterogeneity, the thematic similarities apparent across the dystonic syndrome natural history spectra do enable coordinated approaches. It has been shown, for example, that genetic factors play an important role in the development of dystonic syndromes (12). However, obtaining a genetic diagnosis for dystonia is often difficult because of the lack of appropriate diagnostic tests. A diagnosis is important for the affected patient and his family, though, even when available, the costs of validated tests are not always covered by insurance companies. This is despite the fact that molecular characterization of the sample being critical to a correct diagnosis. This would provide patients with specific genetic counseling, subsequent better care and follow-up. Another important aspect of the genetic diagnosis is its use in research, e.g., giving thought-provoking impulses in order to develop models of the pathomechanism involved (13). Samples, however, are currently only available through highly specialized centers and are stored in a particular system for a population because of the specific research involved.

THE DISCIPLINE OF BIOBANKING

Recently, the paradigm in medicine of "reactive approaches" centered on disease therapy is moving to a more personalized, prognostic, preventative, and contributing approach, focusing on the conservation of health (14). This development is promoted by advances acquired from sequencing of the whole human genome and the rapid development in bioinformatics and analytical laboratory technologies (15). Biobanks, as repositories for the storage of this biological material and its corresponding data, could become important tools and instruments in driving this change in the way health care is delivered.

Instead of the subdivision of complex biological phenomena, interdisciplinary efforts are actually made to address the substantial complexities of human biology and medicine. In these young scientific disciplines, advanced mathematical and statistics strategies support the research into the interactions of individual biological elements. These systems not only can retrospectively analyze biological parameters but can also model *in silico* different interactions. Systems biology research combines "wet laboratory" experimentation with "dry laboratory" predictions of the biological processes (14, 15). All these developments, which took off approximately a decade ago, have helped establish organized biobanking (16, 17). The development of guidelines for the standardization of workflow methods

that ensure sample quality and stability is ongoing (18). When it comes to the future of human medicine and particularly to that of RDs such as dystonia, biobanking may hold the key, and the standardization of biobanking workflows will ensure a promising future.

THE FIELD OF BIOBANKING

Biobanks will typically:

- collect and store biological materials. These should be labeled not only with medical data but also with epidemiological data (e.g., environmental exposure, lifestyle, and occupational information);
- not be static "projects," as biological materials and data are generally collected on a continuous or long-term basis;
- be associated with current (defined) or future (not yet specified) research projects at the time of biospecimen collection;
- apply encoding or be anonymous to ensure donor privacy though under certain circumstances will allow the participants to remain identifiable in order to provide clinically relevant information back to the donor;
- include established governance structures (e.g., ethics review committees) and procedures (e.g., consent) that serve to protect donors' rights and stakeholder interests.

The field of biobanking is, generally speaking, very heterogeneous (16, 17). Although it is difficult to list all distinguishing characteristics of biobanks exhaustively, there are some that can be used to characterize different types of biobanks. These are size, research design, the types of biological samples collected, the method of sample collection, processing and storage, and the disease/research focus. These characteristics will influence the scope of biobank activities, such as the recruitment of donors, the consent procedures, the scale of IT support needed, the structure of its administration, and the potential for commercial usage. In the past, the terminology describing organized collections in medicine has not been consistent. Various terms have been in use to refer to activities involving biobanks/biobanking, such as "human genetic research databases (HGRDs)," "population genetic databases," "biorepositories," or "tissue banks." However, the term "biobank" has now been established.

Multiple biobank formats can be found within the context of medical research. These can be differentiated, based on their design and scientific aim (**Table 2**). However, all biobank formats are linked in some form and, to a certain degree, represent a continuum within the infrastructure supporting all steps in the biomedical research "pipeline" (16, 17).

BIOBANKS FOR DYSTONIA

It is important to access biological materials for scientific research in all medical fields and particularly for research on RDs such as dystonic syndromes, though it is difficult to obtain high quality samples and related clinical data. Biobanks play a major role in providing such materials and data to the scientific community.

Nevertheless, up to date, it is difficult to determine the exact number, nature, and quality of samples from patients with dystonic syndrome included in the various biobanks.

An example of a large initiative that is currently running for the study of dystonia is the "Dystonia Coalition" funded by the National Institutes of Health, USA and aims

TABLE 2 | Biobank designs.

Biobank	Characteristics
Population-based	Find the biomarkers for disease susceptibility within a specific population through prospective molecular epidemiology research. Recruitment of healthy donors, typical of a region, country, or specific ethnicity. DNA isolated from venous blood is the most commonly stored biospecimen. Associated data comprising medical history, physical measurements, and epidemiological data (e.g., lifestyle habits, socioeconomic status).
Disease-orientated	Collection of biological materials, collected within the context of clinical care. Patients will only provide biological material and will eventually provide more samples at follow-up visits during the course of their treatment. A number of different disease-oriented biobank subtypes exist.
Case–control	A selection of matched (age and sex as a minimum) individuals presenting a given disease. These will be matched with compatible healthy controls. Epidemiological case–control studies can be used as biobanks. Population-based biobanks can provide case–control.
Tissue banks	Extremely diverse collections of tissue specimens. Usually invasive sampling followed by cryopreservation. Detailed information on the nature of the underlying disease. Specific form of tissue banks, e.g., formalin-fixed paraffin-embedded specimen collections.
Biobanking within the context of clinical trials	Performed by research organizations and/or investigator-driven clinical trials. Associated with complex clinical and laboratory monitoring data. Examine samples (e.g., blood, urine), which can in turn be integrated into a biobank and used for research. Aim is to identify disease/trial-associated biomarkers.
Other specific biobanking formats	Specific methods are necessary requiring deep experience (e.g., cell cultures of pluripotent cells). Specific research goals (Guthrie cards). Commercial interest with the regard to future regenerative therapies (cord blood).

to establish a centralized biobank of samples for the study of dystonic syndromes. More than 40 participating clinical centers are distributed throughout North America and Europe.[1]

The European counterpart is the Europe Dystonia (ED) group, a group of researchers who have developed a web-based integration of their research activities on the genetics of dystonia.[2] The ED research network presently consists of partners from 16 European countries and Israel. The ED registry and biobank is a collaborative network project supported by all members of the ED research network. It consists of a web-based registry for clinical and genetic data, hosted by the University of Tübingen, and a decentralized biorepository at different research sites.

The structure and the organization of the ED registry fulfill all the requirements of a modern and sustainable biobank system, and in the following sections, the biobank will be explained in more detail.

European Dystonia Registry and Biorepository

Organization

The network includes two types of participating centers, depending on local resources and interests: "Collection only" centers and "Collection-DNA storage" centers. The "Collection only" centers include all Euro-dystonia centers willing to collect clinical data, enter them into the Clinical Dystonia Registry in a standardized way, and draw blood for DNA extraction on patients with dystonia and their consenting relatives, but with no facilities for DNA extraction or storage. In comparison, the "Collection-DNA storage" centers perform all tasks of the "Collection only" center, but, in addition, extract and store samples, grow cells, and make the biospecimen available for research. This combination of centralized and decentralized biobanking combines in a perfect way the strengths of both models: high quality in the control of biospecimens, data management, and operation *via* standardized and harmonized methods of samples extraction and storage between the collecting centers. This combination of both systems is faster, more likely to preserve as many analytes as possible, is suitable for very complex protocols, and leaves space for flexibility and innovation without incurring high setup or transport costs.

Data Handling

Protection of personal data is ensured according to local legal regulations. DNA, personal data, and genetic data are only documented, stored, and analyzed anonymously. Identification of samples and patients may be necessary in order to obtain additional clinical information or to inform the patient that clinically relevant results have been obtained. Identification lists are only available to an authorized clinical investigator at the participating center. Local ethics boards have to approve all procedures. It is important to correlate data and biospecimens from different biobanks, this being crucial in accelerating the pace of translational research. A process of harmonization is crucial in order to share the best practices and procedures in biobanks. This more flexible approach aims at ensuring the effective interchange of valid information and samples (19).

All patients and relatives must be fully informed about the study, in particular, about the voluntary nature of participation and the possibility of withdrawing and having the sample destroyed, at any time. Depending on the local procedure based on the local ethical approval, patients and relatives are also informed that no individual test results will be given, but that information about research results in general can be obtained from the attending physician at the ED center. If clinical genetic testing should become available, based on results of the scientific studies, and the patient has chosen on the consent form to be informed, a formal testing procedure may be suggested to the patient and its relatives according to general guidelines for genetic testing at a certified laboratory. The general procedure in reporting the results of the findings from the use of biospecimens is publishing these for the benefit of the scientific community. Findings that fall outside the research objectives and that have potential health or clinical significance are termed "incidental finding" (20). A debate has recently emerged over the need to return incidental findings, and policies are rapidly being developed to cover actual and future obligations (21). Nevertheless, a harmonized and ethically defensible plan for the return of incidental findings is not yet available, and the final decision is taken according to the evaluation of the responsible clinician.

Ownership

Ownership of (personal) data is a very important issue. Since there are obviously numerous stakeholders in a biobank—the donors, the investigators, the funding agencies, the institution housing the bio-samples, and the ethics review committee—it has been proposed that the institution of the biobank should hold "custodianship" for the use of the resource, and that, as custodian of the samples, should carry numerous responsibilities (22). However, the members of the *European Dystonia Registry and Biorepository* concluded that clinical data and biomaterials remain in the possession of the donor unless national legal regulations determine differently.

Data and Biomaterial Access

All data and DNA-samples are accessible at all times available with no restrictions for the participating centers. Pseudonymized data and DNA-samples are made available to other researchers upon request according to the procedure detailed below. A steering committee has been elected by the majority of the votes of all participating centers of the ED and deals with questions of distribution of the DNA resources for scientific projects on the basis of the procedure outlined below.

Use of Samples

Samples can also be made available to research groups within and outside the ED collaboration. For example, in the case of dystonia, the samples will be used for the study of possible genetic factors in the development and course of the disease, and a research proposal will be submitted to the ED steering committee. The committee then submits a recommendation to the contributing

[1] http://www.rarediseasesnetwork.org/dystonia.
[2] http://dystonia-europe.org.

center based on the scientific merits of the proposal. The steering committee will ensure that all laboratories receiving samples from ED agree in writing that

- samples will be used only for the project applied for;
- samples will not be passed on to other laboratories without express permission; and
- an appropriate publication policy will be guaranteed.

However, the final decision on the use of samples will remain with the local contributing scientists. Contributors will be informed about all study proposals and sample allocations. In some cases, fees can be charged for the maintenance of the biobank.

In addressing the social and ethical challenges of biobanking (23), proper governance is vital to the success of biobanking initiatives: it is crucial in ensuring the safety and protection of participants, in preserving public support and financing, and in safeguarding the availability of biospecimens for research (24, 25). This is especially applicable to RD biobanking efforts because of the rarity and diversity of biomaterials and the role played by patients and patient organizations (13).

Scientific Publications

A major challenge is in how to honor and recognize the effort and the expertise involved in establishing a biobank. Until recently, there was a direct link between the researcher who set up a data set and the background for many publications. This relationship in biobanking, between the custodian and the biobank, is very different, as the biobank has been established as a resource open to others. The custodian of the biobank may or may not, carry out research on material from the biobank. Therefore, the traditional ways of acknowledging researchers through their publications, which may further their careers, become difficult for the custodians of biobanks. Many journals require that data production should be acknowledged, but how this is done is largely left up to individuals who follow the norms that exist in their particular discipline (26).

If results of scientific studies based on the ED collaboration are published, according to good scientific practice, authorship is based on individual contributions. In accordance with the published guidelines of scientific journals, contribution of a limited number of DNA-samples alone is not necessarily sufficient to justify coauthorship. However, regarding all papers based on the use of ED samples, it is proposed to include the following sentence: "and members of Euro-Dystonia Network," with at least one representative of each participating center, which has provided DNA, being listed in an appendix. An accepted significant scientific contribution, justifying coauthorship, would be the contribution of a substantial number of samples with thorough clinical data documentation. This contribution is admittedly hard to evaluate and would need to be assessed case by case.

BENEFITS AND CHALLENGES OF BIOBANKS FOR DYSTONIA

Biobanks for dystonia support the adaptation of laboratory research into clinical applications, the defined goal being to harmonize diagnostic or therapeutic tools for the disease (13, 27). In dystonia, with valuable but limited amounts of biomaterial scattered over a large area, biobanks are a major resource. The purpose of the biobank very much determines its benefits. The purposes vary greatly from generating revenue, supporting scientific discoveries and the understanding the causes of the disease, genetic testing, assessing drug efficacy and treatment, identifying new genes and biomarkers, clinical trials, education, or personalized therapy. Biospecimens held in biobanks have helped researchers and clinicians in their understanding of the mechanism and underlying causes, particularly of RDs, and have also helped with gene identification and the development of diagnostic and therapeutic biomarkers. New genes and new gene mutations have been discovered, thanks to collections of DNA (28–31), as has the development of new diagnostic criteria (32), and the defining of genotype–phenotype correlations (33, 34). Analysis of serum and of plasma has facilitated the identification of new biomarkers (35, 36) and protein profiles (37). Other biospecimens, such as mRNA, stem cells, and tissue, have helped to collect functional data in order to identify other pathways and new therapies to be applied to RDs (38–40).

Three major challenges need to be met in order to increase the effectiveness of biobanks for dystonia: maximizing access for the international scientific community to rare biological samples stored in biobanks across the globe, promoting networking among such biobanks in order to share and harmonize quality standards and procedures and allowing collaboration with dystonia registries and databases, and finally adopting an efficient management model compliant with legal and ethical issues, ensuring biobank sustainability.

Historically, research in dystonia has been highly fragmentary, according to data type, research institution, or dystonic syndrome. There is a limited number of biospecimens for most types of dystonic syndromes, and it may be difficult or impossible to increase the sample number in a short time frame, making these samples extremely precious. Additionally, to achieve usefulness, the quality of the biomaterials and of the associated information is of primary importance (27). Some research biobanks held in laboratories with non-interoperable databases can make it almost impossible to connect genetic data with detailed clinical information or biospecimen availability.

To achieve this, it is important to increase the awareness of dystonia, to increase the number of dystonia registries and biobanks accessible to concerned patients and families, and to expand the availability of biospecimens from these patients. In this context, it is notable that the attitudes toward biobanks are still far from being settled in many countries. In general, there is a cluster of Northern European countries where the prospect of biobank research is greeted enthusiastically, whereas the general public of many Central and Southern European countries is generally more reserved about biobank research, providing tissue samples and granting broad consent for research (41). This reserve has implications for recruitment and also for the running and governance of biobanks. Another particularity with decentralized international biobank network for dystonia is the fact that ethical guidelines and the patient's attitude toward biobanks often differ widely between different countries (42). At the outset, all ethical

considerations should be in line with national guidelines of the patient's country and where the biomaterial has been obtained. However, there exists no global consensus regarding the sharing of biomaterial and data. Eventually, consent will move on to becoming ongoing and dynamic; participants will be able to engage as much as they wish and to change their consent choices over time (20).

THE GENETIC ASPECT

Dystonia is also a very challenging disease from a genetic point of view. First, a number of clearly genetic conditions are still undefined. Second, penetrance of mutations in known genes is low. Third, we observe a broad phenotypic variability in the majority of mutations in known genes. In conclusion, the predictive value of mutations in known genes is low. Even if the mutation is known, we cannot tell whether the person will be affected, and if affected, how seriously. Furthermore, in some countries, prenatal diagnosis is not allowed for mutations with reduced penetrance and uncertain clinical prognosis.

On the other hand, with the introduction of the next-generation sequencing, sequencing of the whole genome in an affordable time frame is now possible. Accordingly, next-generation sequencing increases the pace of discovery of novel genes, even in RDs, tremendously (43). As genetic sequencing becomes cheaper and more accessible, we are about to face an increase of genetic tests in dystonia and subsequently, an increase in unclear variants. In particular, analysis of genes in RDs leads to results associated with extremely limited information about penetrance, phenotype, and prevalence. Moreover, Bell and colleagues recently observed that a high proportion of disease mutations (27%) are incorrectly or incompletely annotated (44). Thus, for many recessive orphan diseases, standard open accessible databases such as HGMD, dbSNP, or OMIM provide insufficient information (44). Identification of potentially underlying genetic causes by means of comprehensive analysis of gene sequences is technically feasible though the clinical interpretation of the functional importance or of the pathogenicity of variants will be challenging for numerous genetic diseases and would require the establishment of an authoritative disease mutation database. Otherwise, the clinical usefulness of comprehensive carrier testing will be limited. The benefit of a transnationally organized biobank, including the molecular characteristic and also results of clinical and paraclinical examinations of the patients and their family members, is based on greater flexibility, particularly regarding the genetic approach. This is mainly because they can support a variety of studies, including cross-sectional studies of genotype–phenotype correlations, case–control studies using a biobank for cases and/or controls, and cohort studies using baseline and follow-up data in a biobank to link genetic variation with health outcomes (45).

FUTURE PERSPECTIVES

Bringing dystonia biobanks to the attention of scientists, clinicians, and patients will require further efforts. These will also be necessary in order to closely link and receive information from specialized diagnostic centers and disease experts, for further qualitative and quantitative progress. It is important that clinical staff should have a clear understanding of the added value of participating in the biobank network. They should be encouraged to collect samples and to update relevant databases. These efforts are a generous contribution to global health research, but they are also a direct path to advancing personal scientific and medical activities (46). It is important to establish an accreditation and evaluation system so as to acknowledge biobanks providing high quality samples and to reward and recognize the scientists who establish and maintain biobanks.

Here, the promotion of collaboration between biobanks and patient associations will not only help collect more samples and associated data and furnish them to researchers but could also help address the ethical and legal challenges, thanks to the underlying agreements based on solidarity.

Sustainability is another important issue facing dystonia biobanking. The pharmaceutical industry, clearly, has little interest in funding small biobanks that contain and exchange small numbers of samples, making specific funding for dystonia biobanks essential. An approach to this problem could be the implementation of a business model in which both cost and revenue are examined. However, the commercialization of the biobank biomaterial and/or clinical data is not always a feasible option. National or institutional regulations, ethical guidelines, or patients refusing informed consent, all prevent any commercialization and limit the willingness of the pharmaceutical industry to get involved.

In order to unify and simplify the practice of biobanking across multiple institutions and different countries, it would be essential to harmonize the legal and regulatory frameworks that apply. Additionally, interoperability and harmonization of dystonia patient registries and dystonia biobanks are critical for linking data, together with time-efficient procedures adapted to the clinical workflow promoting clinical engagement and enhancing diagnostic and therapy development for dystonic syndromes.

CONCLUSION

The challenge for the future of biobanking in RDs as dystonia is how to develop governance that encourages a sustainable international biobanking infrastructure. Presently, the regulatory systems are not harmonized, thus hindering straightforward sharing of samples and data in an ethical and legally compliant manner across national borders. This does not aid cutting-edge research across borders in the most efficient and economical manner. The governance structure for medical research needs to move from being designed around "one-researcher, one-project, one-jurisdiction" model to enable the flow of samples and data between biobanks as part of regional/global networks for research. One way to achieve this is to use information technology to develop e-governance systems that can increase the transparency of the research done and augment existing expert committee review and national systems of oversight. This

will enable dystonia biobanks to become component parts of the health-care structure and a tool to enhance a personalized medicine approach to health care, respecting the participants' fundamental rights and researchers' needs. All future developments should take account of other efforts undertaken elsewhere in the world.

AUTHOR CONTRIBUTIONS

EL: analysis and interpretation of data and drafting the manuscript. KG: analysis and interpretation of data. TG: critical revision of the manuscript for important intellectual content.

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